SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Espranor 2 mg oral lyophilisate.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each oral lyophilisate contains 2 mg of buprenorphine (as hydrochloride).

Each oral lyophilisate contains 0.50 mg aspartame.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral lyophilisate.

White to off-white circular oral lyophilisate with a diameter of 10.3 mm, debossed with ‘M2’ 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.

Treatment with Espranor oral lyophilisate is intended for use in adults and adolescents aged 15 years or over who have agreed to be treated for addiction.

4.2 Posology and method of administration

Posology

Treatment should be under the supervision of a clinician experienced in the management of opiate dependence/addiction.

The route of administration for Espranor is **on the tongue**, not under it.

Espranor is **not interchangeable with other buprenorphine products**. Different buprenorphine products have different bioavailability. Therefore, the dose in mg can differ between products. Once the appropriate dose has been identified for a patient with a certain product (brand), the product cannot readily be exchanged with another product.

Adults and adolescents aged 15 years or over

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 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).

Opioid-dependent drug addicts who have not undergone withdrawal: When treatment starts, the first dose of Espranor should be taken when signs of withdrawal appear, but not less than 6 hours after the patient last used opioids (e.g. heroin; short acting opioids).

Patients receiving methadone: Before beginning Espranor therapy, the dose of methadone must be reduced to a maximum of 30 mg/day. The long half-life of methadone should be considered when starting buprenorphine therapy. The first dose of Espranor should be taken 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.

Because of the partial agonist profile of buprenorphine, the patient should be warned that the first 24 hours of buprenorphine substitution therapy may feel uncomfortable with some mild opiate withdrawal symptoms.

Treatment goals and discontinuation;

Before initiating treatment with Espranor, 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 Espranor, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal (see section 4.4).

Initiation therapy (induction):

The recommended starting dose is 2 mg of Espranor (1 Espranor 2 mg oral lyophilisate). An additional one to two Espranor 2 mg oral lyophilisates may be administered on day one depending on the individual patient's requirement.

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

Dosage adjustment and maintenance:

The dose of Espranor should then be adjusted according to clinical effect with the aim of quickly stabilising the patient. The dosage can be titrated up or down according to assessment of the clinical and psychological status of the patient in steps of 2-6 mg until the minimum effective maintenance dose is achieved, but should not exceed a maximum single daily dose of 18 mg. During the initiation of treatment, daily dispensing of buprenorphine is recommended. After stabilisation, a reliable patient may be given a supply of Espranor sufficient for several days of treatment. It is recommended that the amount of Espranor be limited to 7 days or according to local requirements.

Less than daily dosing:

After satisfactory stabilisation has been achieved the frequency of Espranor 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 may be given 16 mg on alternate days, with no dose on the intervening days. In some patients, after a satisfactory stabilisation has been achieved, the frequency of Espranor 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 18 mg. Patients requiring a titrated daily dose > 8 mg/day may not find this regimen adequate.

Dosage reduction and termination of treatment:

After a satisfactory stabilisation has been achieved, if the patient agrees, the dosage may be reduced gradually to a lower maintenance dose; in some favourable cases, treatment may be discontinued. The availability of Espranor in doses of 2 mg and 8 mg allows for a downward titration of dosage. For patients who may require a lower buprenorphine dose, buprenorphine 1 mg or 0.4 mg sublingual tablets may be used. Patients should be monitored following termination of treatment because of the potential for relapse.

Patients with impaired hepatic function

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 medication (see section 4.5) and/or have existing liver dysfunction are at risk of accelerated liver injury. Regular monitoring of liver function is recommended (see section 4.4).

The effect of hepatic impairment on the pharmacokinetics of buprenorphine is unknown. Since buprenorphine is extensively metabolised in the liver, the plasma levels will be expected to be higher in patients with moderate or severe hepatic impairment.

As Espranor 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 (see section 5.2). Buprenorphine is contraindicated in patients with severe hepatic insufficiency (see section 4.3).

Patients with impaired renal function

Modification of the Espranor dose is not generally 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).

Elderly:

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

Paediatric population:

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

Method of administration

Physicians must warn patients that the oromucosal route of administration is the only effective and safe route for this medicinal product (see section 4.4). The oral lyophilisate is to be placed on the tongue until completely dissolved. Patients should not swallow or consume food or drink until the lyophilisate is completely dissolved. If the oral lyophilizate, or saliva containing buprenorphine are swallowed, the buprenorphine will be metabolised and excreted and have minimal effect. For further information, see the national guidelines for buprenorphine treatment.

Oromucosal administration: the oral lyophilisate should be taken from the blister unit with dry fingers, and placed whole on the tongue until dispersed, which usually occurs within 15 seconds, and then absorbed through the oromucosa. Swallowing should be avoided for 2 minutes. The oral lyophilisate should be taken immediately

after opening the blister. Patients should not consume food or drink for 5 minutes after administration.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Severe respiratory insufficiency
- Severe hepatic impairment
- 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

Warnings

Espranor oral lyophilisate is recommended only for the treatment of opioid drug dependence. It is also recommended that the treatment is prescribed by a physician who ensures comprehensive management of the drug addicted patient(s).

The clinician should consider the risk of abuse and misuse (e.g. IV administrations) particularly at the beginning of the treatment.

Misuse, abuse and diversion:

Buprenorphine can be misused or abused in a manner similar to other opioids, legal or illicit. Some risks of misuse and abuse include overdose, spread of blood borne viral or localised and systemic infections, respiratory depression and hepatic injury. Buprenorphine misused by someone other than the intended patient poses the additional risk of new drug dependent individuals using buprenorphine as the primary drug of abuse, and may occur if the medicine is distributed for illicit use directly by the intended patient or if the medicine is not safeguarded against theft.

Sub-optimal treatment with buprenorphine may prompt medication misuse by the patient, leading to overdose or treatment dropout. A patient who is under-dosed with buprenorphine may continue responding to uncontrolled withdrawal symptoms by self-medicating with opioids, alcohol or other sedative-hypnotics such as benzodiazepines.

To minimise the risk of misuse, abuse and diversion, physicians should take appropriate precautions when prescribing and dispensing buprenorphine, such as to avoid take-home dosing early in treatment, and to conduct patient follow-up visits with clinical monitoring that is appropriate to the patient's need.

Removal of Espranor from the mouth following supervised administration is virtually impossible due to its rapid dispersal on the tongue.

Tolerance and opioid use disorder (abuse and dependence):

Buprenorphine is a partial agonist at the μ (mu)-opiate receptor. 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.

Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids such as Espranor. Abuse or intentional misuse of Espranor 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 Espranor 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 behaviour (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.

Precipitation of opioid withdrawal syndrome:

When initiating treatment with buprenorphine 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 opioids, or if administered less than 24 hours after the last dose of methadone. To avoid precipitating withdrawal, induction with buprenorphine should be undertaken when objective signs of withdrawal are evident (see section 4.2). Conversely, withdrawal symptoms may also be associated with suboptimal dosing.

The risk of serious adverse events such as overdose or treatment dropout is greater if a patient is under-treated with Espranor and continues to self-medicate against withdrawal with opioids, alcohol or other sedative-hypnotics, in particular benzodiazepines.

Respiratory Depression

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

This product should be used with care in patients with asthma or respiratory insufficiency (e.g. chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression or kyphoscoliosis (curvature of spine leading to potential shortness of breath)).

Buprenorphine 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 sight and 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.

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 event reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of hepatic failure. In many cases the presence of pre-existing liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, 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 Espranor, 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.

Hepatic impairment

Hepatic metabolism of buprenorphine may be altered in patients with hepatic impairment, which may give rise to increased plasma concentrations of buprenorphine. A reduction of the buprenorphine dose may be needed (see section 4.2).

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

CNS depression

This product can cause drowsiness, which may be exacerbated by other centrally acting agents, such as alcohol, tranquillisers, sedatives and hypnotics (see section 4.5).

Risk from concomitant use of sedative medicinal products such as benzodiazepines or related medicinal products

Concomitant use of Espranor 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 Espranor 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).

CYP 3A inhibitors

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

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.

Serotonin syndrome

Concomitant administration of Espranor 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.

Espranor contains aspartame

This product contains aspartame (see Section 2 for the quantitative composition). Aspartame is a source of phenylalanine which may be harmful for people with phenylketonuria.

Paediatric population

Espranor is not recommended for use in children below age 15 years due to lack of data on safety and efficacy.

Due to the lack of data in adolescents (aged 15- 18), Espranor should be used only with caution in this age group and more closely monitored during treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Espranor should not be taken together with alcoholic drinks or medications containing alcohol. Alcohol increases the sedative effect of buprenorphine (see section 4.7).

Espranor should be used cautiously when co-administered with:

- Sedative medicine 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 Espranor is abused by deliberate overdose, inhalation or intravenous administration. Patients who are taking Espranor 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).
- Gabapentinoids (gabapentin and pregabalin): The concomitant use of Espranor with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death (see section 4.4).
- 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. This combination increases central nervous system depression. The reduced level of alertness can make driving and using machines hazardous.
- Anticholinergics or medications with anticholinergic activity: 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 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 is an opioid antagonist that can block the pharmacological effects of buprenorphine. Co-administration during buprenorphine treatment should be strongly avoided, due to the potentially dangerous interaction that may precipitate a sudden onset of prolonged and intense opioid withdrawal symptoms For patients currently receiving naltrexone treatment, the intended therapeutic effects of buprenorphine administration may be blocked by naltrexone.
- CYP3A4 inhibitors: an interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in increased Cmax and AUC (area under the curve) of buprenorphine (approximately 50 % and 70 % respectively) and, to a lesser extent, of norbuprenorphine. Patients receiving Espranor 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, macrolide antibiotics, or itraconazole).
- 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 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.
- Concomitant use of monoamine oxidase inhibitors (MAOI): Possible exaggeration of the effects of opioids, based on experience with morphine.
- Serotonergic medicinal products, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).
- Buprenorphine is a CYP3A4 inhibitor *in vitro*. The risk of inhibition *in vivo* at therapeutic concentrations seems low, although it cannot be excluded. When buprenorphine is combined with CYP3A4 substrates the plasma levels of these substrates may increase and dose-dependent side effects may appear.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of buprenorphine 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, high doses, even for a short duration of time, may induce respiratory depression in neonates. During the last three months of pregnancy, chronic use of buprenorphine may be responsible for a withdrawal syndrome in neonates (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 during pregnancy should be assessed by the physician. Buprenorphine should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Breast-feeding

Buprenorphine and its metabolites are excreted in human milk. Therefore, breast-feeding should be discontinued during treatment with Espranor.

4.7 Effects on ability to drive and use machines

Buprenorphine has minor to moderate influence on the ability to drive and use machines when administered to opioid dependent patients. This may cause drowsiness, dizziness or impaired thinking, especially during treatment induction and dose adjustment. When taken together with alcohol or central nervous system depressants, the effect is likely to be more pronounced (see section 4.4 and 4.5). Therefore, caution is advised when driving or operating hazardous machinery in case buprenorphine may affect their ability to engage in such activities.

This medicine can affect your ability to drive.

Do not drive whilst taking this medicine until you know how this medicine affects you.

It may be an offence to drive if your ability to drive safely is affected.

Details regarding a new driving offence concerning driving after drugs have been taken in the UK may be found here: https://www.gov.uk/drug-driving-law.

4.8 Undesirable effects

Summary of the 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 Nervousness Paranoia Thinking abnormal	Drug dependence
Nervous system disorders	Headache	Dizziness Hypertonia Migraine Paraesthesia Somnolence Syncope Tremor	
Eye disorders		Lacrimal disorder Mydriasis	
Cardiac disorders		Palpitations	
Vascular disorder		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	Dental caries
Skin and subcutaneous tissue disorders	Hyperhidrosis	Rash	
Musculoskeletal, connective tissue and bone disorders		Arthralgia Back pain Bone pain Muscle spasms Myalgia Neck pain	

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Frequency not known
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 other selected adverse reactions observed post-marketing

The following is a summary of other post-marketing adverse event reports that are considered serious or otherwise noteworthy, some of which may have only been observed with buprenorphine alone in the treatment of opioid dependence:

- In cases of intravenous drug misuse, local reactions, sometimes septic (abscess, cellulitis), and potentially serious acute hepatitis, and other acute infections such as pneumonia, endocarditis have been reported (see section 4.4).
- In patients presenting with marked drug dependence, initial administration of buprenorphine can produce a drug withdrawal syndrome similar to that associated with naloxone.
- 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 (see section 4.8).
- Hepatic 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 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).
- Hallucination, orthostatic hypotension, urinary retention, syncope and vertigo have been reported.

Drug dependence

Repeated use of Espranor can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on 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 Website: 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.

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 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, following standard intensive care measures, should be instituted. A patent airway and assisted or controlled ventilation must be assured. The patient should be transferred to an environment within which full resuscitation facilities are available.

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 (e.g. 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. Doses of naloxone hydrochloride higher than 10mg may be of limited value and are not recommended in the management 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

Pharmacotherapeutic group: Drugs used in opioid dependence, ATC code: N07BC01

The Espranor oral lyophilisate dosage form is designed to rapidly disperse on the tongue usually in less than 15 seconds.

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

During clinical pharmacological studies in opiate-dependent subjects, buprenorphine demonstrated a ceiling effect on a number of parameters, including positive mood, “good effect”, and respiratory depression.

5.2 Pharmacokinetic properties

Absorption

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

Peak plasma concentrations are achieved around 70 minutes after oromucosal administration and the maximal dose-concentration relationship is linear, between 2 mg and 8 mg.

Distribution

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

Biotransformation and elimination

Buprenorphine is metabolised by 14-N-dealkylation and glucuroconjugation of the parent molecule and the dealkylated metabolite. Clinical data confirm that CYP3A4 is responsible for the N-dealkylation of buprenorphine. N-dealkylbuprenorphine (also known as norbuprenorphine) is a μ (mu) agonist with weak intrinsic activity.

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

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

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).

From teratology studies in rats and rabbits, it was concluded that buprenorphine is not embryotoxic or teratogenic, and it does not have any marked effects on weaning potential. There were no adverse effects on fertility or general reproductive function in rats, although at the highest intramuscular dose (5 mg/kg/day) the mothers experienced some difficulty in parturition and there was a high neonatal mortality.

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

Gelatine
Mannitol
Aspartame (E951)
Mint flavour (051296 TP0551)
Anhydrous citric acid

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package (blister) to protect from light and moisture.

6.5 Nature and contents of container

Unit dose blisters composed of PVC/OPA/Al/OPA/PVC film with Al/PET/paper lidding with 7 or 28 oral lyophilisates, in a cardboard carton.

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

Martindale Pharmaceuticals Ltd
Bampton Road
Romford
Essex
RM3 8UG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL00156/0364

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/06/2023

10 DATE OF REVISION OF THE TEXT

21/11/2024