Espranor (buprenorphine) 2mg and 8mg oral lyophilisate
Prescribing Information

Please refer to the Summary of Product Characteristics (SPC) before prescribing. Presentation: White to off-white circular oral lyophilisate, containing 2 mg or 8 mg of buprenorphine (as hydrochloride). **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. **Dosage and administration:** Administration is oromucosal. *Treatment should be under the supervision of a clinician experienced in the management of opiate dependence/addiction.* ***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.* The route of administration for Espranor is **on the tongue**, not under it. The oral lyophilisate should be placed whole on the tongue, using dry fingers, until dispersed, which usually occurs within 15 seconds. Swallowing should be avoided for 2 minutes and patients should not consume food or drink for 5 minutes after administration. *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. *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 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. *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. *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. In some patients, after a satisfactory stabilisation has been achieved, the frequency of Espranor dosing may be decreased to 3 times a week. 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. *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. *Paediatrics*: The safety and efficacy of buprenorphine in children below the age of 15 years have not been established. No data are available. *Patients with impaired hepatic function:* Baseline liver function tests and documentation of viral hepatitis status is recommended prior to commencing therapy. Espranor pharmacokinetics may be altered in patients with hepatic impairment, therefore lower initial doses and careful dose titration in patients with mild to moderate hepatic impairment are recommended. Buprenorphine is contraindicated in patients with severe hepatic insufficiency. *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). Consult SPC for further information. **Contra-Indications:** Hypersensitivity to the active substance or to any of the excipients. Severe respiratory insufficiency. Severe hepatic impairment. Acute alcoholism or delirium tremens. **Warnings and precautions: 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 administration) particularly at the beginning of the treatment. *Diversion:* Buprenorphine can be misused or abused in a manner similar to other opioids, legal or illicit. Removal of Espranor from the mouth following supervised administration is virtually impossible due to its rapid dispersal on the tongue. *Precipitated Withdrawal:* To avoid precipitating withdrawal, induction with buprenorphine should be undertaken when objective signs of withdrawal are evident. *Respiratory Depression:* A number of cases of death due to respiratory depression have been reported in patients taking buprenorphine. 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. Buprenorphine may cause severe, possibly fatal, respiratory depression in children and non-dependent persons in case of accidental or deliberate 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. 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. A reduction of the buprenorphine dose may be needed. *Renal impairment:* Caution is recommended with dosing patients with severe renal impairment (creatinine clearance < 30 ml/min). *CNS depression:* This product can cause drowsiness, which may be exacerbated by other centrally acting agents, such as alcohol, tranquillisers, sedatives and hypnotics. Athletes should be aware that this medicine may cause a positive reaction to “anti-doping tests”. This product contains aspartame which is a source of phenylalanine, therefore this product 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. *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. **Precautions for Use:** This product can cause orthostatic hypotension. Caution is advised when using buprenorphine in patients with head injury, intracranial lesions, other circumstances where cerebrospinal pressure may be increased or history of seizure, increased intracranial pressure, hypotension, prostatic hypertrophy or urethral stenosis. Opioid-induced miosis, changes in the level of consciousness, or changes in the perception of pain as a symptom of disease may interfere with patient evaluation or obscure the diagnosis or clinical course of concomitant disease. Opioids should be used with caution in patients with myxoedema, hypothyroidism, or adrenal cortical insufficiency (e.g., Addison's disease). Opioids have been shown to increase intracholedochal pressure, and should be used with caution in patients with dysfunction of the biliary tract. Opioids should be administered with caution to elderly or debilitated patients. The concomitant use of monoamine oxidase inhibitors (MAOI) might produce an exaggeration of the effects of opioids, based on experience with morphine. *Consult SPC for further information on this section.* **Interactions:** *Alcoholic drinks or medications containing alcohol:* avoid this combination as alcohol increases the sedative effect of buprenorphine. Espranor should be used cautiously when co-administered with: *Benzodiazepines:* This combination may result in death due to respiratory depression of central origin. *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:* this combination increases central nervous system depression. The reduced level of alertness can make driving and using machines hazardous. *Full opioid agonist:* adequate analgesia may be difficult to achieve. *Naltrexone:* can block the pharmacological effects of

buprenorphine, therefore co-administration should be strongly avoided due to the potentially dangerous interaction that may precipitate a sudden onset of prolonged and intense opioid withdrawal symptoms. *CYP3A4 inhibitors:* Patients should be closely monitored, and may require dose-reduction. *CYP3A4 inducers:* Patients should be closely monitored and the dose of buprenorphine or the CYP3A4 inducer may need to be adjusted accordingly. *Monoamine oxidase inhibitors (MAOI):* Possible exaggeration of the effects of opioids, based on experience with morphine. *Cocaine:* No notable interaction has been observed. *Phenprocoumon*: A suspected interaction resulting in purpura, has been reported. *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. Buprenorphine does not inhibit CYP2C19 in vitro. The inhibitory effect of buprenorphine on other enzymes capable of metabolising substrates in medicinal products has not been studied. **Fertility, Pregnancy and Lactation:** *Fertility*: There are no data on the effects of buprenorphine on human fertility. *Pregnancy:* There are no adequate data from the use of buprenorphine in pregnant women. 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. *Breastfeeding*: Buprenorphine and its metabolites are excreted in human milk. Breastfeeding should be discontinued during treatment with Espranor. **Effects on ability to drive and use machines:** Caution is advised when driving or operating hazardous machinery. **Undesirable effects:** *Summary of the safety profile:* The most commonly reported treatment related adverse reaction reported during the pivotal clinical trials were constipation and symptoms commonly associated with opioid withdrawal (i.e. insomnia, headache, nausea, hyperhidrosis and pain). Some reports of seizure, vomiting, diarrhoea, and elevated liver function tests were considered serious. Most common adverse drug reactions reported during post-marketing surveillance: *Very common:* Insomnia; Headache; Constipation, Nausea; Hyperhidrosis; Drug withdrawal syndrome. *Common:* Anxiety, Depression, Libido decreased, Nervousness, Thinking abnormal; Migraine, Dizziness, Hypertonia, Paraesthesia, Somnolence; Amblyopia, Lacrimation; Hypertension, Vasodilatation; Cough; Abdominal Pain, Diarrhoea, Dyspepsia, Flatulence, Vomiting, Oral hypoaesthesia; Urine Abnormality; Pruritus, Rash, Urticaria; Back Pain, Arthralgia, Muscle spasms, Myalgia; Influenza, Infection, Pharyngitis, Rhinitis; Palpitations; Erectile dysfunction; Asthenia, Chest Pain, Chills, Pyrexia, Malaise, Pain, Oedema peripheral; Liver function test abnormal, Weight decreased; Injury. *Uncommon:* Hypersensitivity; Abnormal dreams, Agitation, Apathy, Depersonalisation, Drug dependence, Euphoric mood, Hostility; Amnesia, Convulsion, Hyperkinesia, Speech disorder, Tremor; Conjunctivitis, Miosis; Hypotension; Asthma, Dyspnoea, Yawning; Mouth ulceration, Tongue discolouration; Albuminuria, Dysuria, Haematuria, Nephrolithiasis, Urinary retention; Acne, Alopecia, Dermatitis exfoliative, Dry skin, Skin mass; Arthritis; Urinary tract infection, Vaginal infection; Anaemia, Leukocytosis, Leukopenia, Lymphadenopathy, Thrombocytopenia; Decreased appetite, Hyperglycaemia, Hyperlipidaemia, Hypoglycaemia; Angina Pectoris, Bradycardia, Myocardial infarction, Tachycardia; Amenorrhoea, Ejaculation disorder, Menorrhagia, Metrorrhagia; Hypothermia; Blood creatinine increased; Heat Stroke. *Description of other selected adverse reactions observed post-marketing:* 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. 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. Hepatic transaminase increase, hepatitis, acute hepatitis, cytolytic hepatitis, jaundice, hepatorenal syndrome, hepatic encephalopathy and hepatic necrosis have occurred. A neonatal drug withdrawal syndrome has been reported among newborns of women who have received buprenorphine during pregnancy. Hallucination, orthostatic hypotension, syncope and vertigo have been reported. Consult SPC for further information. **Product Licence Number:** PL 00156/0364 (2mg), PL 00156/0365 (8mg). **Product Licence Holder:** Martindale Pharmaceuticals Ltd, Bampton Road, Harold Hill, Essex RM3 8UG. **Basic NHS Price:** £6.35 (2mg x 7 oral lyophilisate); £25.40 (2mg x 28 oral lyophilisate); £19.05 (8mg x 7 oral lyophilisate); £76.20 (8mg x 28 oral lyophilisate). **Legal Category:** POM CD. **Further information:** Martindale Pharma, Bampton Road, Romford, RM3 8UG. Tel: 01277266600. **Date of Preparation:** June 2020.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Martindale Pharma. Tel: 01277 266 600 e-mail: drugsafety.uk@ethypharm.com