Mysimba Abbreviated Prescribing Information. Please refer to the Summary of Product Characteristics for full details.

Mysimba 8 mg/90 mg prolonged-release tablet (8 mg naltrexone hydrochloride, equivalent to 7.2 mg naltrexone, and 90 mg bupropion hydrochloride, equivalent to 78 mg bupropion). **Therapeutic indications:** As an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients (≥18 years) with an initial Body Mass Index (BMI) of: ≥ 30 kg/m^2 (obese), or ≥ 27 kg/m^2 (overweight) in the presence of one or more weight-related co-morbidities (e.g., type 2 diabetes, dyslipidaemia, or controlled hypertension). Treatment with Mysimba should be discontinued after 16 weeks if patients have not lost at least 5% of their initial body weight. **Posology:** Initial treatment, the dose should be escalated over a 4-week period as follows: **Week 1:** One tablet in the morning, **Week 2:** One tablet in the morning and one tablet in the evening, **Week 3:** Two tablets in the morning and one tablet in the evening, **Week 4** and onwards: Two tablets in the morning and two tablets in the evening (maximum recommended daily dose). Evaluate the need for continued treatment after 16 weeks and annually thereafter. The cardiovascular risks of Mysimba when given for longer than a year have not been fully determined. Discontinue after one year if patients have not maintained ≥ 5% weight loss; conduct annual assessments to ensure no adverse change in cardiovascular risk before continuing treatment. **Missed dose:** patients should not take an additional dose, but take the next dose at the usual time. **Special populations:** Naltrexone/bupropion should be used with caution in patients **over 65 years of age and is not recommended in patients over 75 years of age**. Naltrexone/bupropion is contraindicated in patients with **end-stage renal failure**. In patients with moderate or severe renal impairment, the maximum recommended daily dose is two tablets (one tablet in the morning and one tablet in the evening). It is recommended that patients with moderate or severe renal impairment initiate treatment with one tablet in the morning for the first week of treatment and escalate to one tablet in the morning and one tablet in the evening from week 2 onwards. For individuals who are at elevated risk for renal impairment, in particular patients with diabetes or elderly individuals, estimated glomerular filtration rate (eGFR) should be assessed prior to initiating therapy with naltrexone/bupropion. Patients with **hepatic impairment:** naltrexone/bupropion is **contraindicated** in patients with **severe hepatic impairment**. For with mild hepatic impairment, the maximum recommended daily dose is two tablets. Degree of hepatic impairment should be assessed using the Child-Pugh score. **Paediatric population children and adolescents below 18:** Contraindicated. **Method of administration:** The tablets should be swallowed whole with some water and preferably with food, and should not be cut, chewed or crushed. **Contraindications:** Hypersensitivity to the active substance(s) or to any of the excipients, uncontrolled hypertension, current seizure disorder or a history of seizures, a known central nervous system tumour, undergoing acute alcohol or benzodiazepine withdrawal, history of bipolar disorder, receiving any concomitant treatment containing bupropion or naltrexone, current or previous diagnosis of bulimia or anorexia nervosa, currently dependent on opioids including opioid-containing medication, treated with opioids agonists used in opioid dependence, or in acute opioid withdrawal, receiving concomitant administration of monoamine oxidase inhibitors (MAOI). **Special warnings and precautions for use:** The safety and tolerability of naltrexone/bupropion should be assessed at regular intervals. **Suicide and suicidal behaviour:** Monitor patients during treatment, particularly during early treatment and dose changes, as bupropion, an antidepressant, may increase risk of suicidal behaviour, particularly in patients aged <25 years. **Seizures and associated conditions:** The co-administration of antipsychotics, antidepressants, antimalarials, tramadol, theophylline, systemic steroids, quinolones and sedating antihistamines may lower the seizure threshold, and the consumption of alcohol during naltrexone/bupropion treatment should be minimised or avoided. Opioid containing medications including analgesics: ensure opioids are stopped for 7-10 days before starting naltrexone/bupropion, and discontinue it at least 3 days before any

necessary opioid use, without increasing the opioid dose beyond standard level. **Allergic reactions have been reported:** A patient should stop taking naltrexone/bupropion and consult a doctor if experiencing allergic or anaphylactoid/anaphylactic reactions during treatment**. Severe cutaneous adverse reactions (SCARs):** Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP), and drug reaction with eosinophilia and systemic symptoms (DRESS) - which can be life-threatening or fatal- have been reported with bupropion containing products. Advise patients of skin reaction signs and symptoms and monitor closely. If signs and symptoms of SCAR occur discontinue naltrexone/bupropion immediately and consider an alternative treatment (as appropriate) Do not restart naltrexone/bupropion treatment. **Elevation of blood pressure** has been observed with naltrexone/bupropion treatment. Measure blood pressure and pulse before starting naltrexone/bupropion and regularly thereafter; discontinue if there are sustained, clinically relevant increases. **Cardiovascular disease:** There is no clinical experience establishing the safety of naltrexone/bupropion in patients with a recent history of myocardial infarction, unstable heart disease or NYHA class III or IV congestive heart failure however use should be with caution. **Brugada Syndrome**: Caution is advised in patients with Brugada syndrome or a family history of cardiac arrest or sudden death. **Hepatotoxicity:** In naltrexone/bupropion completed clinical studies, where naltrexone hydrochloride daily doses ranged from 16 mg to 48 mg, drug-induced liver injury (DILI) was reported. A patient with suspected DILI should stop taking naltrexone/bupropion. **Serotonin Syndrome:** There have been post-marketing reports of serotonin syndrome when co-administered with a serotonergic agent. If concomitant treatment with other serotonergic agents is warranted, careful observation of the patient is advised, and treatment discontinuation should be considered if symptoms develop. Data in animals suggest a potential for abuse of bupropion, however studies in humans and extensive clinical expertise have shown low abuse potential. **Influence on the ability to drive and use machines:** Naltrexone/bupropion has been associated with somnolence and episodes of loss of consciousness. Patients **must be advised to exercise caution while driving or operating** machines during treatment. **Lactose:** Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption use is contraindicated**.** Consult the educational materials, including the Physician Prescribing Checklist, before prescribing. **Patients should be advised to carry the patient card with them at all times. Interaction with other medicinal products and other forms of interaction:** concomitant MAOIs or opioid analgesics must not be used. Drugs metabolised by cytochrome P450 (CYP) enzymes and OCT2 substrates have potential for interaction. **Pregnancy** limited data available and the drug should not be used in pregnant or women trying to become pregnant. **Breast-feeding:** Naltrexone and bupropion and their metabolites are excreted in human milk and use is contraindicated. **Fertility:** No data available. **Undesirable effects:** The most frequent adverse reactions in clinical studies were nausea (very common), constipation (very common), vomiting (very common), dizziness (common), and dry mouth (common). The most frequent adverse reactions leading to discontinuation with naltrexone/bupropion were nausea (very common), headache (very common), dizziness (common) and vomiting (very common). **Overdose:** There is no clinical experience with overdose with combined use of bupropion and naltrexone. **Excipients: Tablet core:** contains Lactose monohydrate (For a full list see the SmPC). **Shelf life**: 30 months. **Storage:** Do not store above 30°C. Nature and contents of container: PVC/PCTFE/PVC/Aluminium blisters. **Pack sizes:** 28, 112 tablets. **MARKETING AUTHORISATION HOLDER: Orexigen Therapeutics Ireland Limited**, 9-10 Fenian Street, Dublin 2, Ireland. **MARKETING AUTHORISATION NUMBER(S):** EU/1/14/988/001-002. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**: **26 March 2015.** Date of latest renewal: **16 January 2020.** Detailed information on this medicinal product is available on www.ema.europa.eu. Adverse events should be reported to Orexigen Therapeutics Ireland

Limited (+356 800 62176) or use the link to report directly to Currax.MI@primevigilance.com.
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