ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Mysimba 8 mg/90 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 8 mg naltrexone hydrochloride, equivalent to 7.2 mg of naltrexone, and 90 mg bupropion hydrochloride, equivalent to 78 mg of bupropion.

Excipient with known effect:
Each prolonged-release tablet contains 73.2 mg of lactose (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet.

Blue, biconvex, round tablet of 12-12.2 mm diameter debossed with "NB-890" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mysimba is indicated, 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 to < 30 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 (see section 5.1).

4.2 Posology and method of administration

Posology

Upon initiating 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

The maximum recommended daily dose of Mysimba is two tablets taken twice daily for a total dose of 32 mg naltrexone hydrochloride and 360 mg bupropion hydrochloride.
The need for continued treatment should be evaluated after 16 weeks (see section 4.1) and re-evaluated annually. The cardiovascular risks of Mysimba when given for longer than a year have not been fully determined. Treatment with Mysimba should be discontinued after one year if patients

have not maintained a loss of at least 5% of their initial body weight (see Section 4.1). Annual assessment should be conducted by the healthcare professional in discussion with the patient when considering treatment continuation to ensure no adverse change in their cardiovascular risk (see Section 4.4) and maintenance of weight loss as defined in this section.

Missed dose
If a dose is missed, patients should not take an additional dose, but take the prescribed next dose at the usual time.

Special populations

Elderly patients (over 65 years)
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 (see sections 4.4, 4.8 and 5.2).

Patients with renal impairment
Naltrexone/bupropion is contraindicated in patients with end-stage renal failure (see section 4.3). In patients with moderate or severe renal impairment, the maximum recommended daily dose for naltrexone/bupropion is two tablets (one tablet in the morning and one tablet in the evening) (see sections 4.4, 4.8 and 5.2). 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. Dose reduction is not necessary in patients with mild renal impairment. 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 (see section 4.3). Naltrexone/bupropion is not recommended in patients with moderate hepatic impairment (see sections 4.4 and 5.2). In patients with mild hepatic impairment, the maximum recommended daily dose for naltrexone/bupropion is two tablets (one tablet in the morning and one tablet in the evening) (see sections 4.4 and 5.2). It is recommended that patients with mild hepatic 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. Degree of hepatic impairment should be assessed using the Child-Pugh score.

Paediatric population
The safety and efficacy of naltrexone/bupropion in children and adolescents below 18 have not yet been established. Therefore, naltrexone/bupropion should not be used in children and adolescents below 18.

Method of administration

Oral use. The tablets should be swallowed whole with some water. The tablets should preferably be taken with food (see section 5.2). The tablets should not be cut, chewed, or crushed.

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
- Patients with uncontrolled hypertension (see section 4.4)
- Patients with a current seizure disorder or a history of seizures (see section 4.4)
- Patients with a known central nervous system tumour
- Patients undergoing acute alcohol or benzodiazepine withdrawal
- Patients with a history of bipolar disorder
- Patients receiving any concomitant treatment containing bupropion or naltrexone
- Patients with a current or previous diagnosis of bulimia or anorexia nervosa
- Patients currently dependent on opioids including opioid-containing medication, patients

treated with opioid agonists used in opioid dependence (e.g., methadone, buprenorphine), or patients in acute opioid withdrawal (see sections 4.4 and 4.5)

- Patients receiving concomitant administration of monoamine oxidase inhibitors (MAOI). At least 14 days should elapse between discontinuation of MAOI and initiation of treatment with naltrexone/bupropion (see section 4.5)Patients with severe hepatic impairment (see sections 4.2 and 5.2)
- Patients with end-stage renal failure (see sections 4.2 and 5.2)

4.4 Special warnings and precautions for use

The safety and tolerability of naltrexone/bupropion should be assessed at regular intervals.

The treatment should be discontinued if there are concerns with the safety or tolerability of ongoing treatment, including concerns about increased blood pressure (see section 4.8).

Suicide and suicidal behaviour

Naltrexone/bupropion contains bupropion. Bupropion is indicated for the treatment of depression in some countries. A meta-analysis of placebo-controlled clinical trials of antidepressants in adult subjects with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in subjects less than 25 years old.

Although in placebo-controlled clinical trials with naltrexone/bupropion for the treatment of obesity in adult subjects, no suicides or suicide attempts were reported in studies up to 56 weeks duration with naltrexone/bupropion, suicidality events (including suicidal ideation) have been reported in subjects of all ages treated with naltrexone/bupropion post-marketing.

Close supervision of patients, particularly those at high risk, should accompany therapy with naltrexone/bupropion especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Seizures

Bupropion is associated with a dose-related risk of seizures, with bupropion sustained release (SR) 300 mg yielding an estimated seizure incidence of 0.1%. Plasma concentrations of bupropion and metabolites of bupropion following single-dose administration of 180 mg of bupropion as naltrexone/bupropion tablets are comparable to concentrations observed after single-dose administration of bupropion SR 150 mg; however, no study has been conducted that determined the concentrations of bupropion and metabolites of bupropion after repeated dosing of naltrexone/bupropion tablets compared to bupropion SR tablets. As it is unknown whether the risk for seizure with bupropion is related to bupropion or a metabolite of bupropion, and there are no data demonstrating comparability of plasma concentrations with repeated dosing, there is uncertainty whether repeated-dose administration naltrexone/bupropion may be associated with a similar rate of seizures as bupropion SR 300 mg. The incidence of seizure in subjects receiving naltrexone/bupropion in clinical trials was approximately 0.06% (2/3,239 subjects) vs. 0.0% (0/1,515 subjects) on placebo. This incidence of seizure, along with incidence of seizure in subjects who received naltrexone/bupropion in a large cardiovascular outcomes trial (CVOT), was no higher than the seizure rate with bupropion as a single agent at approved doses.

The risk of seizures is also related to patient factors, clinical situations, and concomitant medicinal products, which must be considered in the selection of patients treated with naltrexone/bupropion. Naltrexone/bupropion should be discontinued and not restarted in patients who experience a seizure while being treated with the medicinal product. Caution should be used when prescribing naltrexone/bupropion to patients with predisposing factors that may increase the risk of seizure including:

- history of head trauma

- excessive use of alcohol or addiction to cocaine or stimulants
- as treatment with naltrexone/bupropion may result in lowered glucose in patients with diabetes, the dose of insulin and/or oral diabetic medicinal products should be assessed to minimise the risk of hypoglycaemia, which could predispose patients to seizure
- concomitant administration of medicinal products that may lower the seizure threshold, including antipsychotics, antidepressants, antimalarials, tramadol, theophylline, systemic steroids, quinolones and sedating antihistamines

The consumption of alcohol during naltrexone/bupropion treatment should be minimised or avoided.

Patients receiving opioids

Patients must be warned against the concomitant use of opioids during treatment with naltrexone/bupropion (see sections 4.3 and 4.5).

Naltrexone/bupropion must not be administered to patients currently dependent on opioids, including opioid-containing medication or patients treated with opioid agonists used in opioid dependence (e.g., methadone, buprenorphine) or patients in acute opioid withdrawal (see sections 4.3 and 4.5).

Naltrexone/bupropion may be used with caution after opioid use has been stopped for at least 7 to 10 days in order to prevent the precipitation of withdrawal symptoms. When opioid use is suspected, a test may be performed to ensure clearance of opioid medication before starting treatment with naltrexone/bupropion. If opioid therapy is required after treatment initiation, naltrexone/bupropion treatment must be stopped. Serious life-threatening reactions, such as seizure and serotonin syndrome, have been observed after co-administration of naltrexone/bupropion and opioids. Insufficient intra-/post-operative opioid analgesia during treatment with naltrexone/bupropion has been reported.

In patients requiring intermittent treatment with opioids (e.g., due to a surgical procedure), naltrexone/bupropion therapy should be discontinued for a minimum of 3 days before and the opioid dose should not be increased above the standard dose. During naltrexone/bupropion clinical studies, the use of concomitant opioid or opioid-like medicinal products, including analgesics or antitussives were excluded. However, approximately 12% of subjects took a concomitant opioid or opioid-like medicinal product while enrolled in the naltrexone/bupropion clinical studies, the majority of whom continued study treatment without interruption of naltrexone/bupropion dose, without untoward consequences.

Naltrexone/bupropion-induced-opioid receptor blockade should not be compensated by administering large amounts of exogenous opioids as this may lead to fatal overdose or life endangering opioid intoxication (e.g., respiratory arrest, circulatory collapse).

After naltrexone/buproprion treatment is discontinued, patients may be more sensitive to opioids due to diminished tolerance, thus lower doses may be needed.

Allergic reactions

Anaphylactoid/anaphylactic reactions characterised by symptoms such as pruritus, urticaria, angioedema, and dyspnoea requiring medical treatment have been reported in clinical trials with bupropion. In addition, there have been rare spontaneous postmarketing reports of erythema multiforme, and anaphylactic shock associated with bupropion. A patient should stop taking naltrexone/bupropion and consult a doctor if experiencing allergic or anaphylactoid/anaphylactic reactions (e.g., skin rash, pruritus, hives, chest pain, oedema, and shortness of breath) during treatment.

Arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity have been reported in association with bupropion. These symptoms may resemble serum sickness.

Patients should be advised to notify their prescribing physician if they experience these symptoms. If serum sickness is suspected, naltrexone/bupropion should be discontinued.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS) and acute generalised exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with naltrexone/bupropion treatment.
Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, naltrexone/bupropion should be withdrawn immediately and an alternative treatment considered (as appropriate). If the patient has developed a serious reaction such as SJS or AGEP with the use of naltrexone/bupropion, the treatment must not be restarted in this patient at any time.

Elevation of blood pressure

Early, transient mean increases from baseline in systolic and diastolic blood pressure of up to 1 mmHg were observed in naltrexone/bupropion Phase 3 clinical trials. In a cardiovascular outcomes trial (CVOT) of patients at increased risk of a cardiovascular event, mean increases from baseline in systolic and diastolic blood pressure of approximately 1 mmHg compared to placebo were also observed. In clinical practice with other bupropion containing products, hypertension, in some cases severe and requiring acute treatment, has been reported. Furthermore, post-marketing cases of hypertensive crisis have been reported during the initial titration phase with naltrexone/bupropion.

Blood pressure and pulse should be measured prior to initiation of therapy with naltrexone/bupropion and should be assessed at regular intervals consistent with usual clinical practice. If patients experience clinically relevant and sustained increases in blood pressure or pulse rate as a result of naltrexone/bupropion treatment, it should be discontinued.

Naltrexone/bupropion should be given with caution to those patients with controlled hypertension and must not be given to patients with uncontrolled hypertension (see section 4.3).

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. Naltrexone/bupropion should be used with caution in patients with active coronary artery disease (e.g., ongoing angina or recent history of myocardial infarction) or history of cerebrovascular disease.

Brugada syndrome

Bupropion may unmask Brugada syndrome, a rare hereditary disease of the cardiac sodium channel with characteristic ECG changes (right bundle branch block and ST segment elevation in right precordial leads), which may lead to cardiac arrest or sudden death. 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. There have also been cases of elevated liver enzymes from post-marketing reporting. A patient with suspected DILI should stop taking naltrexone/bupropion.

Elderly patients

Clinical studies of naltrexone/bupropion did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. Elderly patients may be more sensitive to the central nervous system adverse reactions of naltrexone/bupropion. Naltrexone and bupropion are known to be substantially excreted by the kidney, and the risk of adverse reactions

to naltrexone/bupropion may be greater in patients with impaired renal function, a condition that is more common in elderly individuals. Due to these reasons, 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.

Renal impairment

Naltrexone/bupropion has not been extensively evaluated in subjects with renal insufficiency. Naltrexone/bupropion is contraindicated in patients with end-stage renal failure. In patients with moderate or severe renal impairment, the maximum recommended daily dose for naltrexone/bupropion should be reduced, as these patients may have higher drug concentrations which could result in an increase in adverse drug reactions (see sections 4.2, 4.8, and 5.2). For individuals who are at elevated risk for renal impairment, in particular, individuals with diabetes or elderly individuals, estimated glomerular filtration rate (eGFR) should be assessed prior to initiating therapy with naltrexone/bupropion.

Hepatic impairment

Naltrexone/bupropion has not been extensively evaluated in subjects with hepatic impairment. Naltrexone/bupropion is contraindicated in patients with severe hepatic impairment, and not recommended in patients with moderate hepatic impairment (see sections 4.2, 4.3, and 5.2). In patients with mild hepatic impairment, the maximum recommended daily dose for naltrexone/bupropion should be reduced, as these patients may have higher drug concentrations which could result in an increase in adverse drug reactions. (see sections 4.2 and 5.2).

Serotonin Syndrome

There have been post-marketing reports of serotonin syndrome, a potentially life-threatening condition, when naltrexone/bupropion was co-administered with a serotonergic agent, such as Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs) and opioids (e.g. tramadol, methadone) (see sections 4.5 and 4.8). If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.
Serotonin syndrome may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g. hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea). If serotonin syndrome is suspected, a discontinuation of therapy should be considered.

Neuropsychiatric symptoms and activation of mania

Activation of mania and hypomania have been reported in patients with mood disorders who were treated with other similar medicinal products for major depressive disorder. No activation of mania or hypomania was reported in the clinical trials evaluating effects of naltrexone/bupropion in obese subjects, which excluded subjects receiving antidepressants. Naltrexone/bupropion should be used cautiously in patients with a history of mania.

Panic attacks, particularly in patients with a history of psychiatric disorders, have been reported with naltrexone/bupropion. The cases occurred mostly during the initial titration phase and following dose changes. Naltrexone/bupropion should be used with caution in patients with a history of psychiatric disorders.

Data in animals suggest a potential for abuse of bupropion. However, studies on abuse liability in humans and extensive clinical experience show that bupropion has low abuse potential.

Influence on the ability to drive and use machines

The use of naltrexone/bupropion has been associated with somnolence and episodes of loss of

consciousness, sometimes caused by seizure. Patients must be advised to exercise caution while driving or operating machines during treatment with naltrexone/bupropion, especially at the beginning of the treatment or during the titration phase. Patients who experience dizziness, somnolence, loss of consciousness or seizure should be advised to avoid driving or operating machines until these adverse effects have resolved. Alternatively, treatment cessation might be considered (see sections 4.7 and 4.8).

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Educational materials

All physicians who intend to prescribe Mysimba must ensure they have received and are familiar with the physician educational material. Physicians must explain and discuss the benefits and risks of Mysimba therapy with the patient as provided in the SmPC and the prescriber guide (Physician Prescribing Checklist).

Patients should be advised to carry the patient card with them at all times, which is provided with each package of Mysimba.

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine oxidase inhibitors (MAOI)

Since monoamine oxidase A and B inhibitors also enhance the catecholaminergic pathways, by a different mechanism from bupropion, naltrexone/bupropion must not be used with MAOI (see section 4.3).

Opioids
Naltrexone/bupropion is contraindicated in patients currently dependent on opioids including opioid-containing medication, patients treated with opioid agonists used in opioid dependence (e.g., methadone, buprenorphine), or patients in acute opioid withdrawal (see sections 4.3 and 4.4). Due to the antagonistic effect of naltrexone at the opioid receptor, patients taking naltrexone/bupropion may not fully benefit from treatment with opioid-containing medicinal products, such as cough and cold remedies, antidiarrhoeal preparations and opioid analgesics.

Drugs metabolised by cytochrome P450 (CYP) enzymes

Bupropion is metabolised to its major active metabolite hydroxybupropion primarily by the cytochrome P450 CYP2B6; thus, the potential exists for interaction when administered with medicinal products that induce or inhibit CYP2B6. Although not metabolised by the CYP2D6 isoenzyme, bupropion and its main metabolite, hydroxybupropion, inhibit the CYP2D6 pathway and the potential exists to affect medicinal products metabolised by CYP2D6.

CYP2D6 substrates
In a clinical study, naltrexone/bupropion (32 mg naltrexone hydrochloride /360 mg bupropion hydrochloride daily) was co-administered with a 50 mg dose of metoprolol (a CYP2D6 substrate). Naltrexone/bupropion increased metoprolol AUC and C_{max} by approximately 4- and 2-fold, respectively, relative to metoprolol alone. Similar clinical drug interactions resulting in increased pharmacokinetic exposure of CYP2D6 substrates have also been observed with bupropion as a single medicinal product with desipramine and venlafaxine.

Co-administration of bupropion with drugs that are metabolised by CYP2D6 isozyme including certain antidepressants (SSRIs and many tricyclic antidepressants, e.g. desipramine, imipramine, paroxetine), antipsychotics (e.g., haloperidol, risperidone and thioridazine), beta-blockers (e.g., metoprolol) and Type 1C antiarrhythmics (e.g., propafenone and flecainide), should be approached

with caution and should be initiated at the lower end of the dose range of the concomitant medicinal product. Although citalopram is not primarily metabolised by CYP2D6, in one study, bupropion increased the C_{max} and AUC of citalopram by 30% and 40%, respectively.

There have been post-marketing reports of serotonin syndrome, a potentially life-threatening condition, when naltrexone/bupropion was co-administered with a serotonergic agent, such as Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs) and opioids (e.g. tramadol, methadone) (see sections 4.4 and 4.8).

Drugs which require metabolic activation by CYP2D6 in order to be effective (e.g., tamoxifen), may have reduced efficacy when administered concomitantly with inhibitors of CYP2D6 such as bupropion. If naltrexone/bupropion is added to the treatment regimen of a patient already receiving a drug metabolised by CYP2D6, the need to decrease the dose of the original medicinal product should be considered, particularly for those concomitant medicinal products with a narrow therapeutic index. When feasible, the option of therapeutic drug monitoring should be considered for medicinal products with a narrow therapeutic index, such as tricyclic antidepressants.

CYP2B6 inducers, inhibitors and substrates
Bupropion is metabolised to its major active metabolite hydroxybupropion primarily by the CYP2B6 isozyme. The potential exists for a drug interaction between naltrexone/bupropion and drugs that induce or are substrates of the CYP2B6 isozyme.

Since bupropion is extensively metabolised, caution is advised when naltrexone/bupropion is co-administered with medicinal products known to induce CYP2B6 (e.g., carbamazepine, phenytoin, ritonavir, efavirenz) as these may affect the clinical efficacy of naltrexone/bupropion. In a series of studies in healthy volunteers, ritonavir (100 mg twice daily or 600 mg twice daily) or ritonavir 100 mg plus lopinavir 400 mg twice daily reduced the exposure of bupropion and its major metabolites in a dose dependent manner by 20 to 80%. Similarly, efavirenz 600 mg once daily for two weeks reduced the exposure of bupropion by approximately 55% in healthy volunteers.

Co-administration of medicinal products that may inhibit the metabolism of bupropion via CYP2B6 isoenzyme (e.g., CYP2B6 substrates: cyclophosphamide, ifosfamide, and CYP2B6 inhibitors: orphenadrine, ticlopidine, clopidogrel), may result in increased bupropion plasma levels and lower levels of active metabolite hydroxybupropion. The clinical consequences of the inhibition of the metabolism of bupropion via CYP2B6 enzyme and the consequent changes in the bupropion-hydroxybupropion ratio are currently unknown, but could potentially lead to reduced efficacy of naltrexone/bupropion.

OCT2 substrates

Bupropion and its metabolites competitively inhibit the OCT2 in the basolateral membrane of the renal tubule responsible for creatinine secretion, in a manner similar to the OCT2 substrate cimetidine. Therefore, mild increases in creatinine observed after long-term treatment with naltrexone/bupropion are likely due to inhibition of OCT2 and not indicative of changes in creatinine clearance. Use of naltrexone/bupropion with other OCT2 substrates (e.g., metformin) in clinical trials did not indicate the need for dose adjustment or other precautions.

Other interactions

Although clinical data do not identify a pharmacokinetic interaction between bupropion and alcohol, there have been rare reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients drinking alcohol during bupropion treatment. There are no known pharmacokinetic interactions between naltrexone and alcohol. The consumption of alcohol during naltrexone/bupropion treatment should be minimised or avoided.

Caution should be used when prescribing naltrexone/bupropion to patients with predisposing factors that may increase the risk of seizure including:

- as treatment with naltrexone/bupropion may result in lowered glucose in patients with

diabetes, the dose of insulin and/or oral diabetic medicinal products should be assessed to minimise the risk of hypoglycaemia, which could predispose patients to seizure
- concomitant administration of medicinal products that may lower the seizure threshold, including antipsychotics, antidepressants, antimalarials, tramadol, theophylline, systemic steroids, quinolones and sedating antihistamines

Naltrexone/bupropion is contraindicated in patients receiving concomitant treatment with monoamine oxidase inhibitors, bupropion or naltrexone, patients undergoing acute alcohol, opioid or benzodiazepine withdrawal, patients currently dependent on opioids (see section 4.3).

Administration of naltrexone/bupropion to patients receiving either levodopa or amantadine concurrently should be undertaken with caution. Limited clinical data suggest a higher incidence of adverse reactions (e.g., nausea, vomiting, and neuropsychiatric adverse reactions – see section 4.8) in patients receiving bupropion concurrently with either levodopa or amantadine.

Administration of naltrexone/bupropion with inhibitors or inducers of UGT 1A2 and 2B7 should be undertaken with caution as these may alter the exposure of naltrexone.

Coadministration of naltrexone/bupropion with digoxin may decrease plasma digoxin levels. Monitor plasma digoxin levels in patients treated concomitantly with naltrexone/bupropion and digoxin. Clinicians should be aware that digoxin levels may rise on discontinuation of naltrexone/bupropion and the patient should be monitored for possible digoxin toxicity.

Naltrexone/bupropion has not been studied in conjunction with alpha-adrenergic blockers or clonidine.

Since bupropion is extensively metabolised, caution is advised when naltrexone/bupropion is co-administered with medicinal products known to inhibit metabolism (e.g. valproate), as these may affect its clinical efficacy and safety.

Naltrexone/bupropion should preferably be taken with food, as it is known that both naltrexone and bupropion plasma concentrations are increased with food and the safety and efficacy data from clinical trials is based on dosing with food.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amounts of data from the use of naltrexone/bupropion in pregnant women. The combination has not been tested in reproductive toxicity studies. Studies with naltrexone in animals have shown reproductive toxicity (see section 5.3); animal studies with bupropion show no clear evidence of reproductive harm. The potential risk for humans is unknown.
Naltrexone/bupropion should not be used during pregnancy or in women currently attempting to become pregnant.

Breast-feeding

Naltrexone and bupropion and their metabolites are excreted in human milk.

Since there is limited information on the systemic exposure to naltrexone and bupropion in infants/newborns being breast-fed, a risk to the newborns/infants cannot be excluded.
Naltrexone/bupropion should not be used during breast-feeding.

Fertility
There are no data on fertility from the combined use of naltrexone and bupropion. No effect on fertility in reproductive toxicity studies have been observed with bupropion. Naltrexone administered orally to rats caused a significant increase in pseudopregnancy and a decrease in pregnancy rates at approximately 30 times the naltrexone dose provided by naltrexone/bupropion. The relevance of

these observations to human fertility is not known (see section 5.3).

4.7 Effects on ability to drive and use machines

Naltrexone/bupropion has influence on the ability to drive and use machines. When driving vehicles or using machines, it should be taken into account that dizziness, somnolence, loss of consciousness and seizure may occur during treatment.

Patients should be cautioned about driving or operating hazardous machinery in case naltrexone/bupropion may affect their ability to engage in such activities (see sections 4.4 and 4.8)

4.8 Undesirable effects

Summary of the safety profile

In clinical studies, 23.8% of subjects receiving naltrexone/bupropion and 11.9% of subjects receiving placebo discontinued treatment due to an adverse reaction. The most frequent adverse reactions for naltrexone/bupropion are 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).

Tabulated list of adverse reactions

The safety profile of naltrexone/bupropion (NB) summarised in Table 1 below is based on clinical studies performed with the fixed-dose combination (adverse reactions at an incidence of at least 0.1% and twice that of placebo) and/or post marketing data sources.The list of terms in Table 2 provides information on the adverse reactions of the individual components naltrexone (N) and bupropion (B) identified in their respective approved SmPCs for different indications.

The frequencies of adverse reactions are ranked according to the following: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 1. Adverse reactions reported in subjects who received naltrexone/bupropion as a fixed-dose combination

System Organ Class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Rare	Decreased haematocrit
		Lymphocyte count decreased
	Not known	Lymphadenopathy
Immune system disorders	Uncommon	Hypersensitivity Urticaria
	Rare	Angioedema
Metabolism and nutrition disorders	Rare	Dehydration
Psychiatric disorders	Common	Anxiety Insomnia
	Uncommon	Abnormal dreams Agitation Mood swings Nervousness Tension Dissociation (feeling spacey)
	Rare	Hallucination
	Not known	Panic attack
	Not known	Affective disorders Aggression Confusional state Delusions Depression Disorientation Disturbance in attention Hostility Loss of libido Nightmares Paranoia Psychotic disorder Suicidal ideation* Suicide attempt Suicidal behaviour
Nervous system disorders	Very common	Headache
	Common	Dizziness Tremor Dysgeusia Lethargy Somnolence
	Uncommon	Intention tremor Balance disorder Amnesia
	Rare	Loss of consciousness Paraesthesia Presyncope Seizure** Syncope

	Not known	Dystonia Memory impairment Parkinsonism Restlessness Serotonin syndrome****
Eye disorders	Not known	Eye irritation Eye pain or asthenopia Eye swelling Lacrimation increased Photophobia
		Vision blurred
Ear and labyrinth disorders	Common	Tinnitus Vertigo
	Uncommon	Motion sickness
	Not known	Ear discomfort Ear pain
Cardiac disorders	Common	Palpitations Heart rate increased
	Uncommon	Tachycardia
Vascular disorders	Common	Hot flush Hypertension***** Blood pressure increased
	Not known	Blood pressure fluctuation
Respiratory, thoracic and mediastinal disorders	Not known	Cough Dysphonia Dyspnoea Nasal congestion Nasal discomfort Oropharyngeal pain Rhinorrhea Sinus disorder Sneezing Yawning
Gastrointestinal disorders	Very common	Nausea Constipation Vomiting
	Common	Dry mouth Abdominal pain upper Abdominal pain
	Uncommon	Abdominal discomfort Dyspepsia Eructation
	Rare	Haematochezia Hernia Lip swelling Lower abdominal pain Dental caries*** Toothache***
	Not known	Diarrhoea Flatulence Haemorrhoids Ulcer

Hepatobiliary disorders	Uncommon	Cholecystitis ALT increased AST increased Hepatic enzyme increased
	Rare	Drug induced liver injury
	Not known	Hepatitis
Skin and subcutaneous tissue disorders	Common	Hyperhidrosis Pruritus Alopecia Rash
	Not known	Acne Erythema multiforme and Stevens Johnson syndrome Cutaneous lupus erythematosus Systemic lupus erythematosus syndrome aggravated Acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders	Rare	Jaw pain
	Not known	Arthralgia Groin pain Myalgia Rhabdomyolysis
Renal and urinary disorders	Uncommon	Blood creatinine increased
	Rare	Micturition urgency
	Not known	Dysuria, Pollakiuria Urinary frequency and/or retention
Reproductive system and breast disorders	Uncommon	Erectile Dysfunction
	Rare	Irregular menstruation Vaginal haemorrhage Vulvovaginal dryness
General disorders and administration site conditions	Common	Fatigue Feeling jittery Irritability
	Uncommon	Asthenia Feeling abnormal Feeling hot Increased appetite Thirst
	Rare	Chest pain Peripheral coldness Pyrexia
	Not known	Chills Energy increased

* Cases of suicidal ideation and suicidal behaviour have been reported during NB therapy (see section 4.4).

** The incidence of seizures is approximately 0.1% (1/1,000). The most common type of seizures is generalised tonic-clonic seizures, a seizure type which can result in some cases in post-ictal confusion or memory impairment (see section 4.4).

*** Toothache and dental caries, while not meeting the criteria for inclusion in this table, are listed based on the subset of patients with dry mouth, in which a higher incidence of toothache and dental caries was observed in subjects treated with NB versus placebo.

**** Serotonin syndrome may occur as a consequence of an interaction between bupropion and a serotonergic medicinal product (e.g., Selective Serotonin Reuptake Inhibitors (SSRIs) or Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs) and opioids (see sections 4.4 and 4.5).

*****Post-marketing cases of hypertensive crisis have been reported during the initial titration phase.

As NB is a fixed combination of two active ingredients, in addition to the terms listed in Table 1, additional adverse reactions seen with one of the active substances may potentially occur. The additional undesirable effects occurring with either of the individual components (bupropion or naltrexone) when used for non-obesity indications are summarized in Table 2.

Table 2. Adverse reactions of the individual components naltrexone and bupropion identified in the respective approved SmPCs.

System Organ Class	Frequency	Adverse Reaction
Infections and infestations	Uncommon	Oral herpes (N)
		Tinea pedis (N)
Blood and lymphatic system disorders	Uncommon	Idiopathic thrombocytopenic purpura (N)
Immune system disorders	Very rare	More severe hypersensitivity reactions including angioedema, dyspnoea/ bronchospasm and anaphylactic shock. Arthralgia, myalgia and fever have also been reported in association with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness. (B)
Metabolism and nutrition disorders	Common	Decreased appetite (N)
	Uncommon	Anorexia (B) Blood glucose disturbances (B)
Psychiatric disorders	Common	Concentration disturbance (B)
	Uncommon	Delusions (B) Depersonalisation (B) Libido disorder (N) Paranoid ideation (B)
Nervous system disorders	Uncommon	Ataxia (B) Incoordination (B)
Eye disorders	Uncommon	Visual disturbance (B)
Cardiac disorders	Common	Electrocardiogram change (N)
Vascular disorders	Uncommon	Postural hypotension (B) Vasodilatation (B)
Respiratory, thoracic and mediastinal disorders	Uncommon	Sputum increased (N)
Gastrointestinal disorders	Common	Taste disorders (B)
Hepatobiliary disorders	Uncommon	Blood bilirubin increased (N) Jaundice (B)
Skin and subcutaneous tissue disorders	Uncommon	Exacerbation of psoriasis (B) Seborrhea (N)
Musculoskeletal and connective tissue disorders	Uncommon	Twitching (B)

Reproductive system and breast disorders	Common	Ejaculation delayed (N)
General disorders and administration site conditions	Uncommon	Weight gain (N)

Description of selected adverse reactions

Seizures
The incidence of seizure in naltrexone/bupropion over the course of the clinical program was 0.06% (2/3,239 subjects). Among the group of subjects treated with naltrexone/bupropion, both cases of seizures were considered as serious and led to treatment discontinuation (see section 4.4). There were no cases of seizures in the placebo group.

Gastrointestinal adverse reactions
The vast majority of subjects treated with naltrexone/bupropion who experienced nausea reported the event within 4 weeks of starting treatment. Events were generally self-limited; the majority of events resolved within 4 weeks and almost all resolved by week 24. Similarly, the majority of events of constipation in subjects treated with naltrexone/bupropion were reported during the dose escalation phase. The time to resolution of constipation was similar between subjects treated with naltrexone/bupropion and subjects treated with placebo. Approximately half of the subjects treated with naltrexone/bupropion who experienced vomiting first reported the event during the dose escalation phase. Time to resolution for vomiting was typically rapid (within one week) and almost all events resolved within 4 weeks. The incidence of these common gastrointestinal adverse reactions in naltrexone/bupropion versus placebo was as follows: nausea (31.8% vs. 6.7%), constipation (18.1% vs. 7.2%), and vomiting (9.9% vs. 2.9%). The incidence of severe nausea, severe constipation, and severe vomiting was low, but was higher in subjects treated with naltrexone/bupropion compared to subjects treated with placebo (severe nausea: naltrexone/bupropion (1.9%), placebo (<0.1%); severe constipation: naltrexone/bupropion (0.6%), placebo (0.1%); severe vomiting: naltrexone/bupropion (0.7%), placebo (0.3%)). No events of nausea, constipation, or vomiting were considered serious.

Other frequent adverse reactions
The majority of subjects treated with naltrexone/bupropion who reported dizziness, headache, insomnia, or dry mouth, first reported these events during the dose escalation phase. Dry mouth may be associated with toothache and dental caries; in the subset of patients with dry mouth, a higher incidence of toothache and dental caries were observed in subjects treated with naltrexone/bupropion compared to subjects treated with placebo. The incidence of severe headache, severe dizziness, and severe insomnia was low, but was higher in subjects treated with naltrexone/bupropion compared to subjects treated with placebo (severe headache: naltrexone/bupropion (1.1%), placebo (0.3%); severe dizziness: naltrexone/bupropion (0.6%), placebo (0.2%); severe insomnia: naltrexone/bupropion (0.4%), placebo (<0.1%)). No events of dizziness, dry mouth, headache, or insomnia in subjects treated with naltrexone/bupropion were considered serious.

Elderly patients
Elderly patients may be more sensitive to some of the central nervous system-related adverse reactions of naltrexone/bupropion (primarily dizziness and tremor). There is an increased incidence of gastrointestinal disorders with higher age categories. Common events leading to withdrawal among elderly were nausea, vomiting, dizziness, constipation.

Type 2 diabetes
Patients with type 2 diabetes treated with naltrexone/bupropion demonstrated a higher incidence of gastrointestinal adverse reactions, primarily nausea, vomiting, and diarrhoea, than subjects without diabetes. Patients with type 2 diabetes may be more prone to these events due to concomitant medicinal product use (e.g., metformin) or may be more likely to have underlying gastrointestinal disorders (e.g., gastroparesis) predisposing to gastrointestinal symptoms.

Renal impairment
Patients with moderate renal impairment had a higher incidence of gastrointestinal and central nervous system-related adverse reactions, thus these patients generally had lower tolerability of naltrexone/bupropion at a total daily dose of 32 mg naltrexone hydrochloride/360 mg bupropion hydrochloride, which is thought to be due to higher plasma concentrations of active metabolites. The

types of tolerability events were similar to the events observed in patients with normal renal function (see sections 4.2, 4.4, and 5.2).

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

Human overdose experience

There is no clinical experience with overdose with combined use of bupropion and naltrexone. The maximum daily dose of combined use of bupropion and naltrexone administered in clinical trials contained 50 mg naltrexone hydrochloride and 400 mg bupropion hydrochloride. The most serious clinical implications of combined use of bupropion and naltrexone overdose are likely related to bupropion.

Bupropion
Acute ingestion of doses in excess of 10 times the maximum therapeutic dose of bupropion (equivalent to approximately in excess of 8 times the recommended daily dose of naltrexone/bupropion) has been reported. Seizure was reported in approximately one third of these overdose cases. Other serious reactions reported with overdoses of bupropion alone included hallucinations, loss of consciousness, sinus tachycardia, and ECG changes such as conduction disturbances (including QRS prolongation) or arrhythmias. Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported mainly when bupropion was part of multiple drug overdoses.

Although most subjects recovered without sequelae, deaths associated with overdoses of bupropion alone have been reported in subjects ingesting large doses of the drug. Serotonin syndrome has also been reported.

Naltrexone
There is limited experience with overdose of naltrexone monotherapy in humans. In one study, subjects received 800 mg naltrexone hydrochloride daily (equivalent to 25 times the recommended daily dose of naltrexone/bupropion) for up to one week showing no evidence of toxicity.

Overdose management

An adequate airway, oxygenation, and ventilation should be ensured. Cardiac rhythm and vital signs should be monitored. EEG monitoring is also recommended for the first 48 hours post-ingestion. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended.

Activated charcoal should be administered. There is no experience with the use of forced diuresis, dialysis, hemoperfusion, or exchange transfusion in the management of combined use of bupropion and naltrexone overdoses. No specific antidotes for combined use of bupropion and naltrexone are known.

Due to the dose-related risk of seizures with bupropion, hospitalisation following suspected overdose with naltrexone/bupropion should be considered. Based on studies in animals, it is recommended that seizures be treated with intravenous benzodiazepine administration and other supportive measures, as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiobesity preparations excluding diet products, centrally acting antiobesity products, ATC code: A08AA62.

Mechanism of action and pharmacodynamic effects

The exact neurochemical appetite suppressant effects of naltrexone/bupropion are not fully understood. The medicinal product has two components: naltrexone, a mu-opioid antagonist, and bupropion, a weak inhibitor of neuronal dopamine and norepinephrine reuptake. These components affect two principal areas of the brain, specifically the arcuate nucleus of the hypothalamus and the mesolimbic dopaminergic reward system.

In the arcuate nucleus of the hypothalamus, bupropion stimulates pro-opiomelanocortin (POMC) neurons that release alpha-melanocyte stimulating hormone (α-MSH), which in turn binds to and stimulates melanocortin 4 receptors (MC4-R). When α-MSH is released, POMC neurons simultaneously release β-endorphin, an endogenous agonist of the mu-opioid receptors. Binding of β-endorphin to mu-opioid receptors on POMC neurons mediates a negative feedback loop on POMC neurons leading to a decrease in the release of α-MSH. Blocking this inhibitory feedback loop with naltrexone is proposed to facilitate a more potent and longer-lasting activation of POMC neurons, thereby amplifying the effects of bupropion on energy balance. Preclinical data suggests that naltrexone and bupropion may have greater than additive effects in this region to reduce food intake when administered together.

Clinical efficacy and safety

The effects of naltrexone/bupropion on weight loss, weight maintenance, waist circumference, body composition, obesity-related markers for cardiovascular and metabolic parameters and patient reported assessments were examined in double-blind, placebo-controlled obesity Phase 2 and Phase 3 trials (BMI range 27-45 kg/m^2) with study durations of 16 to 56 weeks randomised to naltrexone hydrochloride (16 to 50 mg/day) and/or bupropion hydrochloride (300 to 400 mg/day) or placebo.

Effect on weight loss and weight maintenance
Four multicentre, double-blind, placebo-controlled obesity Phase 3 studies (NB-301, NB-302, NB-303 and NB-304) were conducted to evaluate the effect of naltrexone/bupropion in conjunction with lifestyle modification in 4,536 subjects randomised to naltrexone/bupropion or placebo. Treatment was initiated with a dose escalation period. Three of these studies (NB-301, NB-302 and NB-304) designated the primary endpoint at 56 weeks, and 1 study (NB-303) designated the primary endpoint at week 28, but continued for 56 weeks. Studies NB-301, NB-303, and NB-304 included periodic instruction from the study sites to reduce caloric intake and increase physical activity, while NB-302 included an intensive behavioral modification program consisting of 28 group counseling sessions over 56 weeks, as well as a prescribed rigorous diet and exercise regimen. NB-304 evaluated subjects with type 2 diabetes not achieving glycaemic goal of HbA1c <7% (53 mmol/mol) with oral anti-diabetes agents or on diet and exercise alone. NB-303 included a re-randomisation in a blinded manner and the addition of a higher dose of naltrexone (naltrexone hydrochloride 48 mg/bupropion hydrochloride 360 mg) at week 28 to half of the cohort of subjects in the active treatment arm who did not adequately respond to treatment, and as such the primary endpoint comparing weight change with 32 mg naltrexone hydrochloride /360 mg bupropion hydrochloride vs. placebo was evaluated at week 28.

Of the overall population of 4,536 subjects in the naltrexone/bupropion Phase 3 studies, 25% had hypertension, 33% had fasting glucose levels ≥100 mg/dL (5.6 mmol/L) at baseline, 54% had dyslipidaemia at study entry, and 11% had type 2 diabetes.

In the combined Phase 3 studies, the mean age was 46 years, 83% were female, and 77% were White, 18% were Black and 5% were other races. Baseline mean BMI was 36 kg/m^2 and mean waist circumference was 110 cm. The two co-primary endpoints were percent change from baseline body

weight and the proportion of subjects achieving ≥5% total decreased body weight. Data summaries for mean change in body weight reflect the Intent-to-Treat (ITT) population, defined as subjects who were randomised, had a baseline body weight measurement, and had at least one post-baseline body weight measurement during the defined treatment phase, using a last observation carried forward (LOCF) analysis, as well as a completers analysis. Summaries of the proportion of subjects achieving ≥5% or ≥10% reduction in body weight utilise a baseline observation carried forward (BOCF) analysis of all randomised subjects. Overall adherence was similar between trials, and similar between treatment groups. Treatment adherence rates for the integrated Phase 3 studies were: 67% NB vs. 74% placebo at 16 weeks, 63% NB vs. 65% Placebo at 26 weeks, 55% NB vs. 55% placebo at 52weeks.

As seen in Table 2, in the NB-301 study subjects had a mean percent body weight loss of -5.4% while receiving naltrexone/bupropion compared to -1.3% in placebo-treated subjects. Weight loss of at least 5% baseline body weight was observed more frequently for subjects treated with naltrexone/bupropion (31%) compared to placebo (12%) (Table 3). More pronounced weight loss was observed in the cohort of subjects who completed 56 weeks of treatment with naltrexone/bupropion (-8.1%) compared to placebo (-1.8%). Comparable results were seen in the NB-303 study, which was of similar design, with significant weight loss observed in naltrexone/bupropion -treated subjects compared to placebo at the week 28 primary endpoint, and sustained through 56 weeks from baseline (Table 3).

Naltrexone/bupropion was also evaluated in combination with intensive behavioural modification counseling in the NB-302 study. Correspondingly, there was greater mean weight loss from baseline for naltrexone/bupropion treatment (-8.1%) compared to study NB-301 (-5.4%) at week 56, and for placebo (-4.9%) compared to study NB-301 (-1.3%).

The treatment effects observed in obese and overweight subjects with type 2 diabetes mellitus (Study NB-304) were somewhat less pronounced than those observed in the other Phase 3 studies. Naltrexone/bupropion (-3.7%) was significantly ($p<0.001$) more efficacious than placebo (-1.7%) treatment in this population.

Table 3. Mean weight loss (% Change) from baseline to week 56 in naltrexone / bupropion (NB) phase 3 Studies NB-301, NB-302, and NB-304 and from baseline to week 28 in phase 3 study NB-303

	56-Week Data						28-Week Data	
	NB-301		NB-302		NB-304		NB-303	
	NB	PBO	NB	PBO	NB	PBO	NB	PBO
Intent-to-treat analysis set[+]								
N	538	536	565	196	321	166	943	474
Baseline (kg)	99.8	99.5	100.3	101.8	104.2	105.3	100.4	99.4
LS Mean (95% CI) % Change From Baseline	-5.4* (-6.0, -4.8)	-1.3 (-1.9, -0.7)	-8.1* (-8.8, -7.4)	-4.9 (-6.1, -3.7)	-3.7* (-4.3, -3.1)	-1.7 (-2.5, -0.9)	-5.7* (-6.1, -5.3)	-1.9 (-2.4, -1.4)
Completers analysis set[++]								
N	296	290	301	106	175	100	619	319
Baseline (kg)	99.8	99.2	101.2	100.4	107.0	105.1	101.2	99.0
LS Mean (95% CI) % Change From Baseline	-8.1 (-9.0, -7.2)	-1.8 (-2.7, -0.9)	-11.5 (-12.6, -10.4)	-7.3 (-9.0, -5.6)	-5.9 (-6.8, -5.0)	-2.2 (-3.4, -1.0)	-7.8 (-8.3, -7.3)	-2.4 (-3.0, -1.8)

CI, Confidence Interval; LS, Least Squares.

95% confidence intervals calculated as LS Mean ± 1.96 × Standard Error.

[+] Subjects who were randomised, had a baseline body weight measurement, and had at least one post-baseline body weight measurement during the defined treatment phase. Results are based on last-observation-carried-forward (LOCF).

[++] Subjects who have a baseline and a post-baseline body weight measurement and completed 56 weeks (Studies NB-301, NB-302, and NB-304) or 28 weeks (NB-303) of treatment.

* Difference from placebo, $p<0.001$.

Studies NB-301, NB-302, and NB-303 were conducted in subjects who were obese, or overweight or obese with comorbidities. Study NB-302 had a more intensive behavioural modification program, while the primary endpoint of Study NB-303 was at week 28 to allow for re-randomization to different doses in the latter portion of the study. Study NB-304 was conducted in subjects who were overweight or obese and had type 2 diabetes mellitus.

The percentages of subjects with ≥ 5% or ≥ 10% body weight loss from baseline were greater with naltrexone/bupropion compared to placebo in all four Phase 3 obesity trials (Table 4).

Table 4. Percentage (%) of subjects losing ≥5% and ≥10% of body weight from baseline to week 56 in phase 3 studies NB-301, NB-302, and NB-304 and from baseline to week 28 in phase 3 study NB-303

	56-week data						28-week data	
	NB-301		NB-302		NB-304		NB-303	
	NB	PBO	NB	PBO	NB	PBO	NB	PBO
Randomised Population[+]								
N	583	581	591	202	335	170	1001	495
≥5% Weight Loss	31*	12	46**	34	28*	14	42*	14
≥10% Weight Loss	17*	5	30*	17	13**	5	22*	6
Completers[++]								
N	296	290	301	106	175	100	619	319
≥5% Weight Loss	62	23	80	60	53	24	69	22
≥10% Weight Loss	34	11	55	30	26	8	36	9

[+] With baseline observation carried forward (BOCF)

[++] Subjects who have a baseline and a post-baseline body weight measurement and completed 56 weeks (Studies NB-301, NB-302, and NB-304) or 28 weeks (NB-303) of treatment.

* Difference from placebo, $p<0.001$

** Difference from placebo, $p<0.01$

Studies NB-301, NB-302, and NB-303 were conducted in subjects who were obese, or overweight or obese with comorbidities. Study NB-302 had a more intensive behavioural modification program, while the primary endpoint of Study NB-303 was at week 28 to allow for re-randomisation to different doses in the latter portion of the study. Study NB-304 was conducted in subjects who were overweight or obese and had type 2 diabetes mellitus.

Of the subjects with observed data at week 16 in the four Phase 3 clinical trials, 50.8% of those randomised to receive naltrexone/bupropion had lost ≥5% of their baseline body weight, compared to 19.3% of placebo-treated subjects (week 16 Responders). At one year, the average weight loss (using LOCF methodology) among these week 16 Responders who received naltrexone/bupropion was 11.3%, with 55% losing ≥10% bodyweight. Additionally, week 16 Responders who received naltrexone/bupropion had a high retention rate with 87% completing 1 year of treatment. The ≥5% weight loss threshold at week 16 had 86.4% positive predictive value and 84.8% negative predictive value for determining whether a subject treated with naltrexone/bupropion would achieve at least 5% weight loss at week 56. Patients who did not meet the early response criterion were not found to have increased tolerability or safety issues relative to patients who did have a favourable early response.

Effect on cardiovascular and metabolic parameters

Improvements were observed for waist circumference (including subjects with type 2 diabetes), triglycerides, HDL-C and LDL-C/HDL-C ratio for subjects treated with naltrexone/bupropion vs. placebo in all Phase 3 studies (Table 4). Improvements in triglycerides, HDL-C and LDL-C/HDL-C ratio were seen in naltrexone/bupropion-treated subjects diagnosed with baseline dyslipidaemia irrespective of dyslipidaemia treatment. Changes in mean blood pressure are described in section 4.4. In addition, in subjects who did not have type 2 diabetes, there were reductions in fasting insulin and HOMA-IR, a measure of insulin resistance, in naltrexone/bupropion-treated subjects.

Effects on glycaemic control in obese subjects with type 2 diabetes

After 56 weeks of treatment in subjects with type 2 diabetes (NB-304), naltrexone/bupropion exhibited improvements in glycaemic control parameters compared to placebo (Table 4). Greater HbA1c improvement compared to placebo was observed at the first post-baseline measurement (week 16, $p<0.001$). Mean HbA1c change from baseline at week 56 was -0.63% for subjects treated with naltrexone/bupropion compared to subjects on placebo -0.14% ($p<0.001$). In subjects with baseline HbA1c >8% (64 mmol/mol), HbA1c changes at endpoint were -1.1% and -0.5% for

naltrexone/bupropion compared to placebo, respectively. Improvements were observed for fasting glucose, fasting insulin, HOMA-IR and percent of subjects requiring rescue diabetes medicinal products for subjects treated with naltrexone/bupropion vs. placebo.

Table 5. Change in cardiovascular and metabolic parameters from baseline to week 56 in phase 3 studies NB-301, NB-302, and NB-304 and from baseline to week 28 in phase 3 study NB-303

	56-Week Data						**28-Week Data**	
	NB-301		**NB-302**		**NB-304**		**NB-303**	
	NB	**PBO**	**NB**	**PBO**	**NB**	**PBO**	**NB**	**PBO**
Full analysis set+								
N	471	511	482	193	265	159	825	456
Waist circumference, cm	-6.2*	-2.5	-10.0*	-6.8	-5.0*	-2.9	-6.2*	-2.7
Triglycerides, % change	-12.7*	-3.1	-16.6*	-8.5	-11.2*	-0.8	-7.3*	-1.4
HDL-C, mg/dL	3.4*	-0.1	4.1*	0.9	3.0*	-0.3	1.2*	-1.4
LDL-C/HDL-C ratio	-0.21*	-0.05	-0.05*	0.12	-0.15*	0.04	-0.15*	0.07
HbA1c, %	Not applicable				-0.6*	-0.1	Not applicable	
Fasting glucose, mg/dL	-3.2*	-1.3	-2.4	-1.1	-11.9	-4.0	-2.1	-1.7
Fasting insulin, % change	-17.1*	-4.6	-28.0*	-15.5	-13.5	-10.4	-14.1*	-0.5
HOMA-IR, % change	-20.2*	-5.9	-29.9*	-16.6	-20.6	-14.7	-16.4*	-4.2

+ Based on LOCF with the last on-drug observation carried forward.

* P-value <0.05 (nominal values) compared to placebo group.

Studies NB-301, NB-302, and NB-303 were conducted in subjects who were obese, or overweight or obese with comorbidities. Study NB-302 had a more intensive behavioural modification program, while the primary endpoint of Study NB-303 was at week 28 to allow for re-randomisation to different doses in the latter portion of the study. Study NB-304 was conducted in subjects who were overweight or obese and had type 2 diabetes mellitus.

Effect on body composition

In a subset of subjects, body composition was measured using dual energy X-ray absorptiometry (DEXA) (naltrexone/bupropion = 79 subjects and placebo = 45 subjects) and multislice computed tomography (CT) scan (naltrexone/bupropion = 34 subjects and placebo = 24 subjects). The DEXA assessment showed that treatment with naltrexone/bupropion was associated with greater reductions from baseline in total body fat and in visceral adipose tissue than placebo. As expected, naltrexone/bupropion -treated subjects had a greater mean increase from baseline compared with placebo-treated subjects in percent of total body lean mass. These results suggest that most of the total weight loss was attributable to a reduction in adipose tissue, including visceral adipose.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Mysimba in one or more subsets of the paediatric population in obesity (see section 4.2 for information on paediatric use). Naltrexone/bupropion should not be used in children and adolescents.

5.2 Pharmacokinetic properties

The results of a single dose relative bioavailability study in healthy subjects demonstrated that naltrexone/bupropion tablets, when dose adjusted, are bioequivalent based on $AUC_{0-\infty}$ mean ratio and 90% confidence intervals to naltrexone immediate release (IR) or bupropion prolonged release (PR) administered as single agents.

Absorption

Following single oral administration of naltrexone/bupropion tablets to healthy subjects, peak concentrations of naltrexone and bupropion occurred approximately 2 and 3 hours post administration of naltrexone/bupropion, respectively. There were no differences in bioavailability, as measured by AUC, of naltrexone or bupropion when administered in combination compared to each administered alone. However, given the prolonged nature of the drug release for naltrexone/bupropion, C_{max} for naltrexone was markedly reduced compared to the 50 mg naltrexone hydrochloride IR administered alone (about 2-fold difference after dose adjustment). The bupropion C_{max} from naltrexone/bupropion (180 mg bupropion hydrochloride) was equivalent to the C_{max} of bupropion PR (150 mg bupropion hydrochloride), indicating that the bupropion C_{max} achieved with naltrexone/bupropion (360 mg bupropion hydrochloride /day) is comparable to that achieved with commercially available bupropion PR (300 mg bupropion hydrochloride /day) administered alone.

Naltrexone and bupropion are well absorbed from the gastrointestinal tract (>90% absorbed), however, naltrexone has a significant first pass effect thereby limiting systemic bioavailablity, with only 5-6% reaching the systemic circulation intact.

Food effect

When naltrexone/bupropion was given with a high-fat meal the AUC and C_{max} for naltrexone increased 2.1-fold and 3.7-fold and the AUC and C_{max} for bupropion increased 1.4-fold and 1.8-fold, respectively. At steady state, the food effect resulted in AUC and C_{max} increases of 1.7- and 1.9-fold for naltrexone, and 1.1- and 1.3-fold for bupropion, respectively. Clinical experience included varying prandial conditions and supports the use of naltrexone/bupropion tablets with food.

Distribution

The mean volume of distribution at steady state of oral naltrexone and bupropion given as naltrexgone / bupropion, V_{ss} /F, was 5697 liters and 880 liters, respectively.
Plasma protein binding is not extensive for naltrexone (21%) or bupropion (84%) indicating low potential for drug interactions by displacement.

Biotransformation and elimination

Following single oral administration of naltrexone/bupropion tablets to healthy subjects, mean $T_{½}$ elimination half-life was approximately 5 hours for naltrexone and 21 hours for bupropion.

Naltrexone
The major metabolite of naltrexone is 6-beta-naltrexol. Though less potent than naltrexone, 6-beta-naltrexol is eliminated more slowly and thus circulates at much higher concentrations than naltrexone. Naltrexone and 6-beta-naltrexol are not metabolised by cytochrome P450 enzymes and *in vitro* studies indicate that there is no potential for inhibition or induction of important isozymes. Naltrexone is primarily metabolised to 6-beta-naltrexol by the dihydrodiol dehydrogenases (DD1, DD2 and DD4). Other major metabolic routes are the formation of the metabolites 2-hydroxy-3-O-methyl naltrexone and 2-hydroxy-3-O-methyl-6-beta-naltrexol, believed to be mediated by catechol-O-methyl transferases (COMT), and glucuronidation, thought to be mediated by UGT1A1 and UGT2B7.

Naltrexone and its metabolites are excreted primarily by the kidney (37 to 60% of the dose). The derived value for renal excretion of naltrexone after oral administration, adjusting for plasma protein

binding, is 89 mL/min. The enzyme responsible for the main elimination pathway is not known. Faecal excretion is a minor elimination pathway.

Bupropion
Bupropion is extensively metabolised with three active metabolites: hydroxybupropion, threohydrobupropion and erythrohydrobupropion. The metabolites have longer elimination half-lives than bupropion and accumulate to a greater extent. *In vitro* findings suggest that CYP2B6 is the principal isozyme involved in the formation of hydroxybupropion, while CYP1A2, 2A6, 2C9, 3A4 and 2E1 are less involved. In contrast, formation of threohydrobupropion has been reported in the literature to be mediated by 11-beta-hydroxysteroid dehydrogenase 1. The metabolic pathway responsible for the formation of erythrohydrobupropion is unknown.

Bupropion and its metabolites inhibit CYP2D6. Plasma protein binding of hydroxybupropion is similar to that of bupropion (84%) whereas the other two metabolites have approximately half the binding.

Following oral administration of 200 mg of ^{14}C-bupropion hydrochloride in humans, 87% and 10% of the radioactive dose were recovered in the urine and feces, respectively. The fraction of the oral dose of bupropion excreted unchanged was 0.5%, a finding consistent with the extensive metabolism of bupropion.

Accumulation

Following twice daily administration of naltrexone/bupropion, naltrexone does not accumulate, while 6-beta-naltrexol accumulates over time. Based on its half-life, 6-beta-naltrexol is estimated to reach steady state concentrations in approximately 3 days. Metabolites of bupropion (and to a lesser extent unmetabolised bupropion) accumulate and reach steady state concentrations in approximately one week. No study has been performed comparing AUC or C_{max} of naltrexone/bupropion prolonged-release tablets with bupropion PR or naltrexone IR administered as single agents in the multiple dose setting (i.e., under steady state conditions).

Special populations

Gender and race
Pooled analysis of naltrexone/bupropion data revealed no meaningful gender or race-related differences in the pharmacokinetic parameters of bupropion or naltrexone. However, only Caucasian and Black subjects were investigated to a significant extent. No dosage adjustment is necessary based on gender or race.

Elderly people
The pharmacokinetics of naltrexone/bupropion have not been evaluated in the elderly population. Because naltrexone and bupropion metabolic products are excreted in the urine and elderly people are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Naltrexone/bupropion is not recommended in patients over 75 years of age.

Smokers
Pooled analysis of naltrexone/bupropion data revealed no meaningful differences in the plasma concentrations of bupropion or naltrexone in smokers compared to nonsmokers. The effects of cigarette smoking on the pharmacokinetics of bupropion were studied in 34 healthy male and female volunteers; 17 were chronic cigarette smokers and 17 were nonsmokers. Following oral administration of a single 150 mg dose of bupropion hydrochloride, there was no statistically significant difference in C_{max}, half-life, T_{max}, AUC, or clearance of bupropion or its active metabolites between smokers and nonsmokers.

Hepatic impairment
A single-dose pharmacokinetic study has been conducted with naltrexone/bupropion in patients with hepatic impairment. The results from this study demonstrated that in patients with mild hepatic impairment (Child-Pugh scores of 5-6 [Class A]), there was a modest increase in naltrexone concentrations, but concentrations of bupropion and most other metabolites were mostly comparable and no more than doubled to those in patients with normal hepatic function. In patients with moderate (Child-Pugh scores of 7-9 [Class B]) and severe (Child-Pugh scores of 10 or higher [Class C]) hepatic impairment, increases in the maximum concentration of naltrexone of ~6- and ~30-fold were observed for the moderate and severe patients respectively, while increases in bupropion were ~2-fold for both groups. Increases of ~2- and ~4-fold for the area under the curve for bupropion were observed for patients with moderate and severe impairment respectively. There were no consistent changes in naltrexone or bupropion metabolites related to varying degrees of hepatic impairment. Naltrexone/bupropion is contraindicated in patients with severe hepatic impairment (see section 4.3) and is not recommended in patients with moderate hepatic impairment (see section 4.4). In patients with mild hepatic impairment, the maximum recommended daily dose for naltrexone/bupropion should be reduced (see section 4.2).

Renal impairment
A single-dosepharmacokinetic study has been conducted for naltrexone/bupropion in subjects with mild, moderate, and severe renal impairment, compared with subjects with normal renal function. The results from this study demonstrated that the area under the curve for plasma naltrexone and metabolites and for plasma bupropion and metabolites was increased by less than two-fold in patients with moderate and severe renal impairment, and smaller increases were observed for patients with mild renal impairment. Based on these results, there are no dose adjustments recommended for patients with mild renal impairment. For patients with moderate or severe renal impairment, the maximum recommended daily dose for naltrexone/bupropion should be reduced (see section 4.2). Naltrexone/bupropion is contraindicated in end-stage renal failure (see section 4.3).

5.3 Preclinical safety data

The effects of combined bupropion and naltrexone use have not been studied in animals.

Non-clinical data on individual components reveal no special hazard for humans based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. Any effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. However, there is some evidence on hepatotoxicity with increasing dose, since reversible increases of liver enzymes have been found in humans with therapeutic and higher doses (see section 4.4 and 4.8). Liver changes are seen in animal studies with bupropion but these reflect the action of a hepatic enzyme inducer. At recommended doses in humans, bupropion does not induce its own metabolism. This suggests that the hepatic findings in laboratory animals have only limited importance in the evaluation and risk assessment of bupropion.

Reproduction toxicity

Naltrexone (100 mg/kg/day, approximately 30 times the dose of naltrexone in naltrexone/bupropion on a mg/m^2 basis) caused a significant increase in pseudo-pregnancy in the rat. A decrease in the pregnancy rate of mated female rats also occurred. There was no effect on male fertility at this dose level. The relevance of these observations to human fertility is not known.

Naltrexone has been shown to have an embryocidal effect in rats dosed with 100 mg/kg/day of naltrexone (30 times the naltrexone/bupropion dose) prior to and throughout gestation, and in rabbits treated with 60 mg/kg/day of naltrexone (36 times the naltrexone/bupropion dose) during the period of organogenesis.

A fertility study of bupropion in rats at doses up to 300 mg/kg/day, or 8 times the bupropion dose provided by naltrexone/bupropion revealed no evidence of impaired fertility.

Genotoxicity

Naltrexone was negative in the following *in vitro* genotoxicity studies: bacterial reverse mutation assay (Ames test), the heritable translocation assay, CHO cell sister chromatid exchange assay, and the mouse lymphoma gene mutation assay. Naltrexone was also negative in an *in vivo* mouse micronucleus assay. In contrast, naltrexone tested positive in the following assays: Drosophila recessive lethal frequency assay, non-specific DNA damage in repair tests with *E. coli* and WI-38 cells, and urinalysis for methylated histidine residues. The clinical relevance of these equivocal findings is unknown.

Genotoxicity data indicate that bupropion is a weak bacterial mutagen, but not a mammalian mutagen, and therefore is of no concern as a human genotoxic agent. Mouse and rat studies confirm the absence of carcinogenicity in these species.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Cysteine hydrochloride
Microcrystalline cellulose
Hydroxypropyl cellulose
Magnesium stearate
Lactose anhydrous
Lactose monohydrate
Crospovidone type A
Indigo carmine aluminium lake (E132)
Hypromellose
Edetate disodium
Colloidal silicon dioxide

Film-coating:

Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol (3350)
Talc
Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PVC/PCTFE/PVC/Aluminium blisters.

Pack sizes: 28, 112 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Orexigen Therapeutics Ireland Limited
9-10 Fenian Street,
Dublin 2,
D02 RX24
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/988/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 March 2015
Date of latest renewal: 16 January 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

MIAS Pharma Ltd
Suite 1 Stafford House, Strand Road, Portmarnock, Co. Dublin,
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State where Mysimba is marketed, all healthcare professionals who are expected to prescribe Mysimba are provided with a prescriber guide and all patients treated with Mysimba are provided with a patient card. Prior to launch of Mysimba in each Member State the Marketing Authorisation Holder (MAH) must agree the content and format of the prescriber guide with the National Competent Authority.

The prescriber guide shall contain the following key elements:
- a reminder of the indication and the need to discontinue treatment if there are concerns with the safety or tolerability of ongoing treatment, or if after 16 weeks patients have lost less than 5% of their initial body weight or if during the annual assessment of patients who have not maintained the loss of at least 5% of their initial body weight;
- a reminder of the contraindications, warnings and precautions as well as patient characteristics that place patients at higher risk of adverse reactions to Mysimba, to help ensure appropriate patient selection.

The patient card shall contain the following key elements:

- Inform health care professionals that you are using Mysimba in case of surgery. Mysimba may block the effect of opioids, which may be used during and after surgery as part of anaesthesia and pain treatment.
- Your doctor may advise you to stop taking Mysimba at a minimum of 3 days prior to surgery.
- Carry the patient card with you at all times.
- Always read the package leaflet carefully.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Interventional post-authorisation safety study (PASS): In order to further characterise the long-term cardiovascular safety, including the occurrence of major adverse cardiovascular events (MACE) related to naltrexone hydrochloride extended release (ER) and bupropion hydrochloride ER combination in the treatment of patients with obesity or who are overweight, the MAH should submit the results of the prospective, randomised, double-blind, placebo-controlled study CVOT-3 – INFORMUS.	Submission of final study report by 31 December 2028

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Mysimba 8 mg/90 mg prolonged-release tablets
naltrexone hydrochloride/bupropion hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 8 mg naltrexone hydrochloride, equivalent to 7.2 mg of naltrexone, and 90 mg bupropion hydrochloride, equivalent to 78 mg of bupropion.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 prolonged-release tablets
112 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Do not cut, chew or crush.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Orexigen Therapeutics Ireland Limited
9-10 Fenian Street,
Dublin 2,
D02 RX24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/988/001 112 tablets
EU/1/14/988/002 28 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

mysimba
8 mg/90 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Mysimba 8 mg/90 mg prolonged-release tablets
naltrexone hydrochloride/bupropion hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Orexigen

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PATIENT CARD

PATIENT CARD

Mysimba

prolonged-release tablets

naltrexone hydrochloride/bupropion hydrochloride

- Inform health care professionals that you are using Mysimba in case of surgery. Mysimba may block the effect of opioids, which may be used during and after surgery as part of anaesthesia and pain treatment.
- Your doctor may advise you to stop taking Mysimba at a minimum of 3 days prior to surgery.
- Carry the patient card with you at all times.
- Always read the package leaflet carefully.

Please complete this section or ask your doctor to do it
Name:
Doctor's Name:
Doctor's telephone:

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Mysimba 8 mg/90 mg prolonged-release tablets
naltrexone hydrochloride/bupropion hydrochloride

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Mysimba is and what it is used for

Mysimba contains 2 active substances: naltrexone hydrochloride and bupropion hydrochloride and is used in obese or overweight adults to manage weight together with a reduced calorie diet and physical exercise. This medicine works on areas on the brain involved in the control of food intake and energy expenditure.

Obesity in adults over 18 years of age is defined as a body mass index of greater than or equal to 30 and overweight in adults over 18 years of age is defined as a body mass index greater than or equal to 27 and less than 30. The body mass index is calculated as the measured body weight (kg) divided by the measured height squared (m^2).

Mysimba is approved for use in patients with an initial body mass index of 30 or greater; it can also be given to those with a body mass index between 27 and 30 if they have additional weight-related conditions such as controlled high blood pressure (hypertension), type 2 diabetes or high levels of lipid (fat) in the blood.

Mysimba may be discontinued by your doctor after 16 weeks if you have not lost at least 5 percent of your initial body weight. Your doctor may also recommend stopping treatment if you have not maintained the loss of at least 5 percent of your initial body weight after 1 year of treatment or if there are concerns about increased blood pressure, or other concerns with the safety or tolerability of this medicine.

2. What you need to know before you take Mysimba

Do not take Mysimba:
- if you are allergic to naltrexone, to bupropion or to any of the other ingredients of this medicine (listed in section 6);

- if you have an abnormally high blood pressure (hypertension) that is not controlled using a medicinal product;
- if you have a condition that causes fits (seizures) or if you have a history of fits;
- if you have a brain tumour;
- if you are usually a heavy drinker and you have just stopped drinking alcohol, or are going to stop while you are taking Mysimba;
- if you have recently stopped taking sedatives or medicines to treat anxiety (especially benzodiazepines), or if you are going to stop them while you are taking Mysimba;
- if you have or have had a bipolar disorder (extreme mood swings);
- if you are using any other medicines which contain bupropion or naltrexone;
- if you have an eating disorder or had one in the past (for example, bulimia or anorexia nervosa);
- if you are currently dependent on opioids, or taking opioids for the treatment of dependence (for example methadone or buprenorphine), or you are going through acute withdrawal (cold turkey);
- if you are taking medicines for depression or Parkinson's disease called monoamine oxidase inhibitors (MAOIs) or have taken them in the last 14 days;
- if you have severe liver disease;
- if you have endstage kidney disease.

Warnings and precautions
Talk to your doctor or pharmacist before taking Mysimba.
This is important because some conditions make it more likely that you could have side effects (see also section 4).

If you feel **depressed, contemplate suicide, have a history of attempting suicide, panic attacks or any other mental health problems,** you should inform your doctor before taking this medicine.

Fits (seizures)
Mysimba has been shown to cause fits (seizures) in up to 1 in 1,000 patients (see also section 4). You should inform your doctor before taking this medicine:
- if you have had a serious head injury or head trauma;
- if you regularly drink alcohol (see "Mysimba with alcohol");
- if you regularly use medicines to help you to sleep (sedatives);
- if you are currently dependent on or addicted to cocaine or other stimulating products;
- if you have diabetes for which you use insulin or oral medicines that may cause low sugar levels in your blood (hypoglycaemia); or
- if you are taking medicines that may increase the risk of fits (see "Other medicines and Mysimba").

If you have a fit (seizure), you should stop taking Mysimba and consult your doctor immediately.

Hypersensitivity reactions
You should stop taking Mysimba immediately and consult your doctor if you are experiencing any symptoms of an **allergic reaction** such as swelling of the throat, tongue, lips, or face, difficulty swallowing or breathing, dizziness, fever, rash, pain in the joints or in the muscles, itching or hives after taking this medicine (see also section 4).

Serious skin reactions, including Stevens-Johnson syndrome and acute generalised exanthematous pustulosis (AGEP), have been reported in association with Mysimba treatment. Stop using Mysimba and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.

You should talk to your doctor, especially if:
- you have **high blood pressure** before taking Mysimba, because it can become worse. You will have your blood pressure and heart rate measured before you start taking Mysimba and while you are taking it. If your blood pressure or heart rate increases significantly, you may need to

stop taking Mysimba.

- you have uncontrolled **coronary artery disease** (a heart disease caused by poor blood flow in the blood vessels of the heart) with symptoms such as angina (characterised by chest pain) or a recent heart attack.
- you already have or have had a condition affecting the circulation of blood in the brain (**cerebrovascular disease**).
- you have any **liver problems** before you start Mysimba.
- you have any **kidney problems** before you start Mysimba.
- if you have a history of **mania** (feeling elated or over-excited, which causes unusual behaviour). you are taking medicines for **depression**, the use of these medicines together with Mysimba can lead to serotonin syndrome, a potentially life-threatening condition (see "Other medicines and Mysimba" in this section and section 4.)

Brugada syndrome
- if you have a condition called Brugada syndrome (a rare hereditary syndrome that affects the heart rhythm) or if cardiac arrest or sudden death occurred in your family.

Older People
Use caution when taking Mysimba, if you are 65 years or older. Mysimba is not recommended if you are over 75 years.

Children and adolescents
No studies have been conducted in children and adolescents under the age of 18. Therefore Mysimba should not be used in children and adolescents below 18 years.

Other medicines and Mysimba
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Do not take Mysimba with:
- **Monoamine oxidase inhibitors** (medicines to treat depression or Parkinson's disease) such as phenelzine, selegiline, or rasagiline. You must stop taking these medicines for at least 14 days before starting Mysimba (see "Do not take Mysimba").
- **Opioid-containing medicines** for example to treat cough and cold (such as mixtures containing dextromethorphan or codeine), opioid addiction (such as methadone or buprenorphine), pain (for example, tramadol, morphine or codeine), diarrhoea (for example, paregoric). You must have stopped taking any opioid medicines at least 7-10 days before starting Mysimba. Your doctor may carry out a test to ensure that your body has cleared these medicines before starting your treatment.
  If you require treatment with opioids (for example during surgery) while taking Mysimba, you should stop taking Mysimba at least 3 days before starting the treatment with opioids or a surgical procedure. Naltrexone contained in Mysimba blocks the effects of opioids for several days after you stop taking Mysimba.
  Taking Mysimba together with medicines for treating depression and opioids may cause serious life-threatening reactions, such as serotonin syndrome and seizure (see section 2. Tell your doctor if…), (see "Possible side effects").
  If you take higher doses of opioids to overcome these effects of naltrexone, you may suffer from an acute opioid intoxication which may be life threatening. After you stop treatment with Mysimba you may be more sensitive to low doses of opioids (see "Do not take Mysimba").

Tell your doctor if you are taking any of the following medicines, as your doctor will closely monitor you for side effects:

- Medicines that may, when used alone or in combination with naltrexone/bupropion, increase the **risk of fits** such as:
  - medicines for depression and other mental health problems;

- steroids (except drops, creams, or lotions for eye and skin conditions or inhalers for breathing disorders such as asthma);
- medicines used to prevent malaria;
- quinolones (antibiotics such as ciprofloxacine to treat infections);
- theophylline (used in the treatment of asthma);
- antihistamines (medicines to treat hayfever, itch, and other allergic reactions) that cause sleepiness (such as chlorphenamine);
- medicines to lower sugar levels in your blood (such as insulin, sulphonylureas such as glyburide or glibenclamide, and meglitinides such as nateglinide or repaglinide);
- medicines to help you to sleep (sedatives such as diazepam).

- Medicines to treat **depression** (such as amitriptyline, desipramine, imipramine, venlafaxine, paroxetine, fluoxetine, citalopram, escitalopram) or other mental health problems (such as risperidone, haloperidol, thioridazine). Mysimba may interact with some medicines used for treatment of depression and you may experience a so-called serotonin syndrome. Symptoms are mental status changes (e.g. agitation, hallucinations, coma), and other effects, such as body temperature above 38°C, increase in heart rate, unstable blood pressure, and exaggeration of reflexes, muscular rigidity, lack of coordination and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea) (see section 4.)
- Some medicines used to treat **high blood pressure** (beta-blockers such as metoprolol, and clonidine, a centrally acting antihypertensive);
- Some medicines used to treat **irregular heart rhythm** (such as propafenone, flecainide);
- Some medicines used to treat cancer (such as cyclophospamide, ifosphamide, tamoxifen);
- Some medicines for **Parkinson's disease** (such as levodopa, amantadine or orphenadrine);
- Ticlopidine or clopidogrel, mainly used in the treatment of **heart disease or stroke**;
- Medicines used in the treatment of **HIV infection and AIDS**, such as efavirenz and ritonavir;
- Medicines used to treat **epilepsy** such as valproate, carbamazepine, phenytoin or phenobarbital.

Your doctor will closely monitor you for side effects and/or may need to adjust the dose of the other medicines or Mysimba.

Mysimba may make other medicines less effective when taken at the same time:

- **If you take digoxin for your heart**

If this applies to you, tell your doctor. Your doctor may consider adjusting the dose of digoxin.

Mysimba with alcohol

Excessive use of alcohol while being treated with Mysimba might increase the risk for fits (seizures), mental disorder events or might reduce alcohol tolerance. Your doctor may suggest you do not drink alcohol while you are taking Mysimba, or try to drink as little as possible. If you do drink a lot now, do not just stop suddenly, because that may put you at risk of having a fit.

Pregnancy and breast-feeding

Mysimba should not be used during pregnancy, or in women currently planning to become pregnant, or while breast-feeding.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

Ask your doctor for advice before you drive and operate machines since Mysimba might make you feel dizzy and sleepy which may weaken your ability to concentrate and react.

Do not drive, use any tools or machines, or perform dangerous activities until you know how this medicine affects you.

If you experience fainting, muscle weakness or fits during treatment, do not drive or use machines.

In case of doubt, check with your doctor, who might consider to interrupt the treatment depending on your situation.

Mysimba contains lactose (a type of sugar)
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take Mysimba

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The initial dose is usually one tablet (8 mg naltrexone hydrochloride / 90 mg bupropion hydrochloride) once a day in the morning. The dose will be gradually adapted as follows:

- **Week 1:** One tablet once a day in the morning
- **Week 2:** Two tablets every day, one in the morning and one in the evening
- **Week 3:** Three tablets every day, two in the morning and one in the evening
- **Week 4 and onward:** Four tablets every day, two in the morning and two in the evening

The maximum recommended daily dose of Mysimba is two tablets taken twice a day.
After 16 weeks and each year after your treatment initiation, your doctor will evaluate whether you should continue to take Mysimba.

If you have problems with your **liver** or **kidney**, or if you are **older than 65**, and depending on the severity of your problems, your doctor may carefully consider whether this medicine is suitable for you or recommend that you take a different dose, and monitor you more closely for potential side effects. Your doctor may test your blood before initiating treatment with Mysimba if you have high blood sugar (diabetes) or if you are older than 65, so that your doctor can decide if you should take this medicine or if you need to take a different dose.

This medicine is for oral use. Swallow your tablets whole. Do not cut them, chew them or crush them. The tablets should preferably be taken with food.

If you take more Mysimba than you should
If you take too many tablets, you may be more likely to have a fit or other side effects similar to those described in section 4 below. **Do not delay,** contact your doctor or your nearest hospital emergency department immediately.

If you forget to take Mysimba
Skip the missed dose and take your next dose at the next usual time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Mysimba
You may need to take Mysimba for at least 16 weeks to have its full effect. **Do not stop taking Mysimba without talking to your doctor first.**

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Tell your doctor straight away, if you notice any of the following serious side effects:

- **Suicidal thoughts and feeling depressed**
  Frequency of the side effects suicide attempts, suicidal behavior, suicidal thoughts and feeling depressed are not known and cannot be estimated from the available data in people taking Mysimba.

There have been reports of depression, suicidal thoughts, and suicide attempts during treatment with Mysimba. If you have thoughts about harming yourself or other distressing thoughts, or if you are depressed and notice that you feel worse or develop new symptoms, **contact your doctor or go to a hospital straight away.**

- **Fits (seizures):**
  Rare - may affect up to 1 in 1,000 people taking Mysimba with risk of having a fit.
  Symptoms of a fit include convulsions and usually loss of consciousness. Someone who has had a fit may be confused afterwards and may not remember what has happened. Fits are more likely if you take too much, if you take some other medicines or if you are at a higher than usual risk of fits (see section 2).
- **Erythema multiforme and Stevens Johnson Syndrome**
  Not known - frequency cannot be estimated from the available data in people taking Mysimba.
  Erythema multiforme is a severe condition of the skin that may affect the mouth and other parts of the body, with red, often itchy spots starting on the limbs. Stevens Johnson Syndrome is a rare skin condition with severe blisters and bleeding in the lips, eyes, mouth, nose and genitals.
- **Acute generalised exanthematous pustulosis**
  Not known - frequency cannot be estimated from the available data in people taking Mysimba.
  A red, scaly widespread rash with bumps under the skin and blisters accompanied by fever. The symptoms usually appear at the initiation of treatment
- **Rhabdomyolysis**
  Not known - frequency cannot be estimated from the available data in people taking Mysimba.
  Rhabdomyolysis is an abnormal breakdown of muscle tissue which can lead to kidney problems. Symptoms include severe muscle cramps, muscle pain or muscle weakness.
- **Lupus skin rash or worsening of lupus symptoms**
  Not known - frequency cannot be estimated from the available data in people taking Mysimba.
  Lupus is an immune system disorder affecting the skin and other organs. If you experience lupus flares, skin rash or lesions (particularly on sun-exposed areas) while taking Mysimba, contact your doctor straight away, as it might be necessary to stop the treatment.
- **Serotonin syndrome**, that can manifest as mental status changes (e.g. agitation, hallucinations, coma), and other effects, such as body temperature above 38°C, increase in heart rate, unstable blood pressure, and exaggeration of reflexes, muscular rigidity, lack of coordination and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea), while taking Mysimba together with medicines used for treatment of depression (such as paroxetine, citalopram, escitalopram, fluoxetine and venlafaxine and opioids (see section 2.)
  Not known - frequency cannot be estimated from the available data in people taking Mysimba)

Other side effects include:

Very common side effects (may affect more than 1 in 10 people):
- Feeling sick (nausea), being sick (vomiting)
- Constipation
- Headache

Common side effects (may affect up to 1 in 10 people):
- Anxiety
- Dizziness, feeling of dizziness or “spinning” (vertigo)
- Feeling shaky (tremor)
- Difficulty in sleeping (make sure you do not take Mysimba near to bedtime)
- Changes in the taste of food (dysgeusia), dry mouth
- Difficulty concentrating
- Feeling of tiredness (fatigue) and sleepiness, drowsiness or lack of energy (lethargy)
- Ringing in the ears (tinnitus)
- Fast or irregular heartbeat
- Hot flush
- Increased blood pressure (sometimes severe)
- Pain in the upper part of the abdomen
- Pain in the abdomen

- Excessive sweating (hyperhidrosis)
- Rash, itching (pruritus)
- Hair loss (alopecia)
- Irritability
- Feeling jittery

Uncommon side effects (may affect up to 1 in 100 people):
- Hives (uticaria)
- Hypersensitivity
- Abnormal dreams
- Feeling nervous, feeling spacey, tension, agitation, mood swings, Tremor of the head or a limb which increases when trying to perform a particular function (intention tremor)
- Balance disorder
- Loss of memory (amnesia), Tingling or numbness of the hands or feet
- Motion sickness
- Burping
- Abdominal discomfort
- Indigestion
- Inflammation of the gallbladder (cholecystitis)
- Increased creatinine levels in the blood (indicating loss of kidney function)
- Increased liver enzymes and bilirubin levels, liver disorders
- Difficulty in getting or keeping an erection
- Feeling abnormal, weakness (asthenia)
- Thirst, feeling hot
- Chest pain
- Increased appetite, weight gain

Rare side effects (may affect up to 1 in 1,000 people):
- Low amount of certain white blood cells (Lymphocyte count decreased)
- Decreased haematocrit (indicating loss of red blood cell volume)
- Swelling of eyelids, face, lips, tongue or throat, which can cause great difficulty in breathing (angioedema)
- Excessive loss of body water (dehydration)
- Hallucinations
- Fainting, almost fainting (presyncope), loss of consciousness
- Fits
- Passage of fresh blood through the anus usually in or with stool (haematochezia)
- Projection of an organ or the tissue encompassing an organ through the wall of the cavity that normally contains it (hernia)
- Toothache
- Dental caries, cavities
- Pain in the lower part of the abdomen
- Injury to the liver due to drug toxicity
- Jaw pain
- A disorder characterised by a sudden compelling urge to urinate (micturition urgency)
- Irregular menstrual cycle, vaginal bleeding, dryness of the female vulva and vagina
- Coldness of extremities (hands, feet)

Not known side effects (frequency cannot be estimated from the available data):
- Swollen glands in the neck, armpit or groin (lymphadenopathy)
- Mood disorders
- Irrational ideas (delusions)
- Psychosis
- Feeling of acute and disabling anxiety (panic attack)
- Loss of sexual desire
- Feeling hostile
- Severe suspiciousness (paranoia)
- Aggression

- Attention disturbance
- Nightmares
- Confusion, disorientation
- Memory impairment
- Restlessness
- Muscle stiffness, uncontrolled movements, problems with walking or coordination
- Blurred vision, eye pain, eye irritation, eye swelling, watery eyes, increased sensitivity to light (photophobia)
- Ear pain, ear discomfort
- Difficulty in breathing
- Nasal discomfort, congestion, runny nose, sneezing, sinus disorder
- Sore throat, disorder of the voice, cough, yawning Haemorrhoids,
- ulcer
- Diarrhoea
- Passing wind (flatulence)
- Hepatitis
- Acne
- Groin pain
- Muscle pain
- Joint pain Abnormally frequent urination, painful urination
- Chills
- Increased energy

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Mysimba

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after "EXP". The expiry date refers to the last day of that month.

Do not store above 30°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Mysimba contains
- **The active substances are** naltrexone hydrochloride and bupropion hydrochloride. Each tablet contains 8 milligrams of naltrexone hydrochloride, equivalent to 7.2 milligrams of naltrexone, and 90 milligrams of bupropion hydrochloride, equivalent to 78 milligrams of bupropion.
- **The other ingredients (excipients) are:**
- **Tablet core:** microcrystalline cellulose, hydroxypropyl cellulose, lactose anhydrous, lactose monohydrate (see section 2 "Mysimba contains lactose"), cysteine hydrochloride, crospovidone type A, magnesium stearate, hypromellose, edetate disodium, colloidal silicon dioxide, and indigo carmine aluminium lake (E132). **Film-coating:** poly(vinyl alcohol), titanium dioxide (E171), macrogol (3350), talc and indigo carmine aluminium lake (E132).

What Mysimba looks like and contents of the pack
Mysimba prolonged-release tablets are blue, biconvex, round tablets debossed with "NB-890" on one

side. Mysimba is available in packs containing 28 or 112 tablets. Not all pack sizes may be marketed.

Patient Card: handling information
With the packaging of Mysimba you will find a Patient Card that includes important safety information for you and your doctors. Carry the patient card with you at all times.

Marketing Authorisation Holder and Manufacturer

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.