Summary of the risk management plan for Mysimba, prolonged-release tablets (naltrexone hydrochloride/bupropion hydrochloride)

This is a summary of the risk management plan (RMP) for Mysimba. The RMP details important risks of Mysimba, how these risks can be minimised, and how more information will be obtained about Mysimba 's risks and uncertainties (missing information).

Mysimba's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Mysimba should be used.

This summary of the RMP for Mysimba should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Mysimba's RMP.

I. The medicine and what it is used for

Mysimba is authorised as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients (see SmPC for the full indication). It contains Naltrexone HCl/Bupropion HCl as the active substance and it is given orally.

Further information about the evaluation of Mysimba's benefits can be found in Mysimba's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage *http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003687/human_med_001845.jsp&mid=WC0b01ac058001d124*

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Mysimba together with measures to minimise such risks and the proposed studies for learning more about Mysimba's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

The risk minimization measures for Mysimba are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Mysimba is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Mysimba are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Mysimba. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	• Seizures • Interaction with MAOIs, opioid analgesics, drugs that inhibit, induce or are substrates of CYP2B6, and drugs metabolised by CYP2D6 • Transient increases in blood pressure or heart rate • Hypersensitivity reactions including severe reactions like Stevens-Johnson Syndrome • Neuropsychiatric symptoms • Hepatotoxicity • Use in patients with hepatic impairment • Use in patients with moderate or severe renal impairment
Important potential risks	• Suicidality in patients with depression • Off-label use and abuse potential • Congenital malformations
Missing information	• Use during pregnancy • Data on long-term / chronic use beyond 1 year

II.B Summary of important risks

Important Identified Risk – SEIZURES	
Evidence for linking the risk to the medicine	Data from bupropion hydrochloride product information and the literature indicate that bupropion hydrochloride is associated with a dose-related risk of seizures (Zyban SmPC 2018). At doses of Wellbutrin SR (prolonged release [PR]) up to a dose of 300 mg/day, the incidence of seizure is approximately 0.1% (1/1,000) and increases to approximately 0.4% (4/1,000) at the maximum recommended dose (in the US) of 400 mg/day. The bupropion hydrochloride PR dose of 360 mg/day in the NB tablet has been demonstrated to have a comparable Pharmacokinetics profile (Cmax and AUC) to that of commercially available 300 mg/day doses of bupropion hydrochloride PR. Consistent with this pharmacokinetic comparability to currently available doses of 300 mg/day bupropion hydrochloride PR, the rate of seizure in the NB programme was <0.1%.
Risk factors and risk groups	Risk groups or risk factors for seizures could not be determined based on information from the NB phase 2/3 clinical trials programme given the near absence of cases (n=2). <u>Bupropion HCl historical experience</u> Antidepressant and antipsychotic drugs are known to reduce seizure threshold and provoke epileptic seizures; therefore, seizure is an expected safety concern with bupropion HCl therapy that is highly

	dose-dependent. As described previously, data from bupropion HCl product information and the literature indicate that bupropion HCl is associated with a dose-related risk of seizures. For Wellbutrin SR (prolonged release) at doses up to 300 mg/day, the incidence of seizure is approximately 0.1% (1/1,000) and increases to approximately 0.4% (4/1,000) at the maximum recommended dose of 400 mg/day. Risk groups for seizures after bupropion HCl therapy include patients with pre-existing or prior history of seizure disorders, central nervous system (CNS) tumour, and those undergoing abrupt withdrawal from alcohol or any medicinal product known to be associated with risk of seizures on withdrawal (in particular benzodiazepines and benzodiazepine-like agents). Risk factors for seizures following bupropion HCl therapy include factors that can lower the seizure threshold, such as concomitant administration of other medicinal products known to lower the seizure threshold (e.g. antipsychotics, antidepressants, antimalarials, tramadol, theophylline, systemic steroids, quinolones and sedating antihistamines), alcohol abuse, history of head trauma, diabetes treated with hypoglycaemic agents or insulin, use of stimulants or anorectic products, and medical history of diseases which contribute to electrolyte imbalances such as anorexia/bulimia. <u>Naltrexone HCl historical experience</u> Although naltrexone HCl is used as an aid in the treatment of alcoholism, it not uniformly helpful to all patients, and the expected effect of the drug is a modest improvement in the outcome of conventional treatment. This, together with the fact that NB contains a lower dose of naltrexone HCl than that used therapeutically for alcoholism, makes it unlikely that NB treatment would induce an acute withdrawal from alcohol or any associated alcohol withdrawal seizures.
Risk minimisation measures	**Routine risk minimisation measures** SmPC includes current seizure disorder or a history of seizures on the list of contraindications (Section <u>4.3</u>). The SmPC also includes text regarding seizures in Section 4.4 "Special warnings and precautions for use" and sections 4.5, 4.8 and 4.9 The package leaflet includes the following text in Section 2: *Do not take NB if you have a condition that causes fits (seizures) or if you have a history of fits.* It also includes further text regarding seizures in Section 2. Mysimba is subject to medical prescription. **Additional risk minimisation measures** Physician educational kit, to reinforce indication and ensure appropriate patient selection, which contains: SmPC Physician Prescribing Checklist
Specific clinical measures	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 (SmPC section 4.4).
Additional pharmacovigilance activities	NB-451 and NB-452.

Important Identified Risk – INTERACTION WITH MAOIS, OPIOID ANALGESICS, DRUGS THAT INHIBIT, INDUCE OR ARE SUBSTRATES OF CYP2B6, AND DRUGS METABOLISED BY CYP2D6	
Evidence for linking the risk to the medicine	Certain other medicines may affect, or be affected, by Mysimba. These include certain medicines used to treat depression (MAOIs) certain strong painkillers (opioid–containing painkillers), or medicines which affect the enzymes in the liver that break down the active substances in Mysimba. If medicines are affected by Mysimba this means that either they will not be as effective, or their effect may be increased, resulting in side effects. Similarly, some medicines may cause Mysimba to be less effective or may increase the risk of side effects.
Risk factors and risk groups	Obese patients with their co-morbidities and the need for treating them. Therapy of comorbidities results in administration of concomitant medications to NB and the potential of drug interactions. Obese patients requiring treatment with opioids, for example for pain relief, and patients with opioid dependence.
Risk minimisation measures	**Routine risk minimisation measures** SmPC includes patients receiving concomitant MAOIs, patients currently dependent on chronic opioids or opiate agonists (e.g., methadone), or patients in acute opiate withdrawal, on the list of contraindications (Section 4.3). The SmPC also includes text regarding patients receiving opioid analgesics in Section 4.4 "Special warnings and precautions for use". Section 4.5 further details interactions. The package leaflet includes the following text in Section 2: *Do not take NB:* *- if you have a bipolar disorder (extreme mood swings);* *- if you are currently dependent on chronic opiates or opiate agonists (for example methadone), 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;* *You should talk to your doctor, especially if you have a history of mania (feeling elated or over-excited, which causes unusual behaviour).* It also includes further text regarding MAOI and opiate in Section 2. Mysimba is subject to medical prescription. **Additional risk minimisation measures** Physician educational kit, to reinforce indication and ensure appropriate patient selection, which contains: SmPC Physician Prescribing Checklist
Additional pharmacovigilance activities	NB-451 and NB-452.

Important Identified Risk – TRANSIENT INCREASES IN BLOOD PRESSURE OR HEART RATE	
Evidence for linking the risk to the medicine	Bupropion HCl has been shown to have sympathomimetic properties due to its effects as a relatively weak dopamine and norepinephrine reuptake inhibitor. Bupropion HCl, treatment has been reported to

	be associated with mild increases in blood pressure. Its observed haemodynamic profile has been well established and is described in the bupropion HCl product information.
Risk factors and risk groups	Risk groups or risk factors associated with transient increases in blood pressure following NB therapy include patients with history of high blood pressure and patients with uncontrolled hypertension.
Risk minimisation measures	**Routine risk minimisation measures** The SmPC includes uncontrolled hypertension on the list of contraindications (Section 4.3). There is also further text regarding hypertension in Section 4.4 (Special warnings and precautions for use) and section 4.8. Mysimba is subject to medical prescription. **Additional risk minimisation measures** Physician educational kit, to reinforce indication and ensure appropriate patient selection, which contains: • SmPC • Physician Prescribing Checklist
Specific clinical measures	Measurement of blood pressure and pulse prior to initiation of therapy and at regular intervals consistent with usual clinical practice; treatment discontinuation in case of clinically relevant and sustained increase in blood pressure or pulse rate (SmPC section 4.4.
Additional pharmacovigilance activities	NB-452 NB-CVOT study 2

Important Identified Risk – HYPERSENSITIVITY INCLUDING SEVERE REACTIONS LIKE STEVENS-JOHNSON SYNDROME	
Evidence for linking the risk to the medicine	Overall, mild or moderate hypersensitivity reactions such as itchy rash (urticaria) are seen in up to 1 patient in 10 taking medicines containing bupropion, but severe hypersensitivity reactions have been very rarely reported (in up to 1 in 10,000 patients). Symptoms of severe hypersensitivity reactions include itching, a rash, swelling of eyelids, face, lips, tongue or throat, and/or chest pain, and difficulty in breathing requiring medical treatment.
Risk factors and risk groups	Risks groups for hypersensitivity were not identified in the NB clinical development programme. A review of the literature did not reveal any risk factors for hypersensitivity in the target population.
Risk minimisation measures	**Routine risk minimisation measures** The SmPC includes *Hypersensitivity to the active substance(s) or to any of the excipients* on the list of contraindications (Section 4.3). There is also further text regarding allergic reactions in Section 4.4 (Special warnings and precautions for use) and section 4.8. The package leaflet for NB states: Section 2 *Do not take NB:* *if you are allergic to naltrexone, to bupropion or to any of the other ingredients of this medicine.* *PL section 4* Mysimba is subject to medical prescription. **Additional risk minimisation measures** None
Additional pharmacovigilance activities	NB-451

Important Identified Risk – NEUROPSYCHIATRIC SYMPTOMS	
Evidence for linking the risk to the medicine	Effects on mood and mental function have been reported when bupropion or naltrexone are taken alone. With regards to bupropion, anxiety is listed as a common AE in the Zyban SmPC (Section 4.8 Undesirable effects). Safety of bupropion using prescription event monitoring methodology in the UK population (n=11,735) was evaluated and it was found that the incidence proportion of agitation over a 3-year follow-up period (2000-2003) was 0.32% (Boshier 2003). No SAEs related to anxiety were reported to the French PV database of bupropion (Beyens 2008). However, anxiety was listed as a very common AE for naltrexone (Nalorex SmPC 2018, Section 4.8) which suggests an incidence proportion of >10%. Depression was of special interest because of historical concerns surrounding antidepressant treatment and suicidal ideation and behaviour.
Risk factors and risk groups	Subjects ≥65 years of age in the Total NB group experienced more Psychiatric Disorders SOC events (27.4%) compared to placebo (6.3%) although the sample size was small for Total NB and placebo, respectively, and primarily diabetic. This was reflected primarily in insomnia (11.3% Total NB, 3.1% placebo) and depression (6.5% Total NB, 3.1% placebo). There did not appear to be a clinically significant sex, ethnic, race or other subgroup difference in the incidence of Psychiatric events reported between the Total NB and placebo groups. Risk group or risk factors for mania could not be determined from the NB clinical development programme given the absence of cases. A review of the literature could not identify risk factors for mania in the target population. In the *general population* of patients treated with antidepressants, *Gao et al* reported an inverse association was found through multivariable regression analysis between the number of mood episodes in the last 12 months and treatment-emergent mania (OR=0.90). Factors such as gender, bipolar subtype, a lifetime history of comorbid anxiety disorder, substance use disorder, or psychosis, and age of mood disorder onset were not found to significantly predict the occurrence of mania following antidepressant treatment. Antidepressants have been associated with an increased risk of treatment-emergent mania or hypomania, particularly in patients with bipolar disorder who have a short illness duration, multiple past antidepressant trials, and past experience of switch with at least one antidepressant. *Bupropion* and NB are contraindicated in patients with history of bipolar disorder as it may precipitate a manic episode during the depressed phase of their illness (NB SmPC section 4.3). Specific risk groups or risk factors for depression were not identified in the NB clinical development programme. An association between depression and obesity has been well-established in clinical studies. *Petry et al* reported a 3% to 5% increased risk of depression for each unit increase in BMI. Depression occurs in obese individuals as a result of a complex interaction between genetic and environmental factors such as severity of depression, severity of obesity, gender, socio-economic status (SES), gene-by-environment interactions and childhood experiences, as well as eating and physical activity, teasing, disordered eating and stress. In women obesity is associated with major depression; however, in men there is an inverse relationship

	between depression and obesity, and there is no relationship with SES. Moreover, adverse childhood experiences can promote the development of both depression and obesity. In the NB clinical trials programme, patients with a history of anxiety or depression had a higher incidence of anxiety-type events than patients without a history of anxiety or depression.
Risk minimisation measures	Routine risk minimisation measures The SmPC includes *patients with a history of bipolar disorder* and p*atients with a current or previous diagnosis of bulimia or anorexia nervosa* on the list of contraindications (Section 4.3). There is also further text regarding Neuropsychiatric Symptoms and Activation of Mania in Section 4.4 (Special warnings and precautions for use) and section 4.8. The package leaflet for NB states: Section 2 *Do not take NB:* • *if you have a bipolar disorder (extreme mood swings);* • *if you have an eating disorder or had one in the past (for example, bulimia or anorexia nervosa);* There is also further text regarding mental health problems and mania in Section 2 and section 4. Mysimba is subject to medical prescription. **Additional risk minimisation measures** Physician educational kit, to reinforce indication and ensure appropriate patient selection, which contains: • SmPC • Physician Prescribing Checklist
Additional pharmacovigilance activities	NB-451 and NB-452

Important Identified Risk – HEPATOTOXICITY	
Evidence for linking the risk to the medicine	Naltrexone (one of the active substances in Mysimba) may cause damage to the liver when given in excessive doses (around 10 or more times the recommended daily dose in Mysimba). Such effects have not been observed in studies with Mysimba. Naltrexone US prescribing information notes that naltrexone has the capacity to cause hepatocellular injury when given in excessive doses (daily doses >300 mg). However, according to the EU product information, the administration of daily doses of naltrexone up to 800 mg (equivalent to 25 times the recommended daily dose of NB32) for 7 days did not cause side effects (Nalorex® FR product information, 2011).
Risk factors and risk groups	Analysis of the NB integrated safety dataset found no significant differences in the incidence of hepatic-related adverse events between NB and placebo groups with respect to age, race, obesity class, the occurrence of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values >3 X the upper limit of normal (ULN) during the study, 5% weight loss at endpoint, alcohol use, or diabetes history. Changes in hepatic function tests have been described in obese elderly patients receiving naltrexone at doses higher than recommended (up to 300 mg/day) for the treatment of alcoholism.
Risk minimisation measures	**Routine risk minimisation measures** The SmPC provides the maximum recommended daily dose of NB (Section 4.2) and includes text regarding hepatotoxicity in Section 4.4 (Special warnings and precautions for use) and Section 5.3 (Preclinical safety data) and section 4.8.

	PL section 4. Mysimba is subject to medical prescription. **Additional risk minimisation measures** Physician educational kit, to reinforce indication and ensure appropriate patient selection, which contains: • SmPC • Physician Prescribing Checklist
Additional pharmacovigilance activities	NB-451 and NB-452

Important Identified Risk – USE IN PATIENTS WITH HEPATIC IMPAIRMENT	
Evidence for linking the risk to the medicine	At the time of approval of NB, the understanding of the potential effects of hepatic impairment came from data from available literature and approved product information on individual components bupropion HCl and naltrexone HCl. From the experience of existing products, mild or moderate hepatic impairment seem to increase the exposure of bupropion and hydroxybupropion (two- to three-fold) and to increase the PK variability between individual patients in terms of bupropion plasma levels.
Risk factors and risk groups	Obesity/overweight increases the risk for liver disease. Obesity often results in the accumulation of fat cells in the liver. Fatty Acids that are secreted by these fat cells can cause a reaction in the body that destroys healthy liver cells and results in scarring (sclerosis) and liver damage. Non-alcoholic fatty liver disease (NAFLD) is a disease of the liver characterised by fatty infiltration with or without inflammation (non-alcohol steatohepatitis or NASH). Previously thought to be benign, it can progress to fibrosis and cirrhosis. It can also result in liver cancer. The risk for developing liver disease varies, depending on the underlying cause and the particular condition. General risk factors for liver disease include alcoholism, diabetes, exposure to industrial toxins, heredity (genetics), and long-term use of certain medications. Patients with obesity also have an increased risk of primary liver malignancies and increased body mass index is a predictor of decompensation of liver cirrhosis.
Risk minimisation measures	**Routine risk minimisation measures** The SmPC provides the maximum recommended daily dose of NB (Section 4.2), includes patients with severe hepatic impairment on the list of contraindications (Section 4.3) and includes text regarding use in hepatic impairment in Section 4.4 (Special warnings and precautions for use) and Section 5.2 (Pharmacokinetic properties). The package leaflet for NB states in <u>Section 2:</u> Do not take Mysimba if you have severe liver disease. You should talk to your doctor, especially if: You have any liver problems before you start Mysimba. There is also further text regarding liver in section 3. Specific clinical measures: Dose adjustment for patients with mild hepatic impairment (weak 1: one tablet in the morning; from week 2 onwards: one tablet in the morning and one tablet in the evening). Mysimba is subject to medical prescription.

Important Identified Risk – USE IN PATIENTS WITH SEVERE OR MODERATE RENAL IMPAIRMENT	
Evidence for linking the risk to the medicine	The identified potential effects of renal impairment come from data obtained in a single dose pharmacokinetic study of NB, along with from available literature and approved product information on bupropion HCl and naltrexone HCl.
Risk factors and risk groups	Obesity is a potent risk factor for the development of kidney disease. It increases the risk of developing major risk factors for chronic kidney disease (CKD), like diabetes and hypertension, and it has a direct impact on the development of CKD and end-stage renal disease (ESRD). In individuals affected by obesity, a likely compensatory mechanism of hyperfiltration occurs to meet the heightened metabolic demands of the increased body weight. The increase in intraglomerular pressure can damage the kidney structure and raise the risk of developing CKD in the long term. Although the exact mechanisms whereby obesity may worsen or cause CKD remain unclear. A high BMI is one of the strongest risk factors for new-onset CKD. In a population-based study of 5.24 million individuals from the United Kingdom, a 5 kg/m^2 higher BMI was associated with a 25% higher risk of kidney cancers, with 10% of all kidney cancers attributable to excess weight. Elderly people represent also another risk group 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 in this population.
Risk minimisation measures	**Routine risk minimisation measures** The SmPC provides the maximum recommended daily dose of NB (Section 4.2), includes patients with end-stage renal failure on the list of contraindications (Section 4.3) and includes text regarding use in renal impairment in Section 4.4 (Special warnings and precautions for use) and Section 5.2 (Pharmacokinetic properties). The package leaflet for NB states in Section 2. Do not take Mysimba if you have endstage kidney disease. You should talk to your doctor, especially if you have any kidney problems before you start Mysimba. There is also further text regarding kidney in section 3. Specific clinical measures: Dose adjustments for patients with moderate or severe renal impairment (weak 1: one tablet in the morning; from week 2 onwards: one tablet in the morning and one tablet in the evening). For individuals who are at elevated risk for renal impairment, in particularly patients with diabetes or elderly individuals, estimated glomerular filtration rate (eGFR) should be assessed prior to initiating therapy with NB. Mysimba is subject to medical prescription.

Important Potential Risk – SUICIDALITY IN PATIENTS WITH DEPRESSION	
Evidence for linking the risk to the medicine	All antidepressants carry class SmPC statements for risk of suicide and suicidal behaviour. Overall, the antidepressants class statements for this risk indicated it is predominantly established in paediatric, adolescent and young adult ($\leqslant$ 24 years) patients with depression. However, based upon the ongoing evaluation of NB post-marketing data, the SmPC has been updated to clarify that suicidality events have been observed in NB treated patients of all ages.

	it is considered a potential risk because bupropion has antidepressant actions and depression may worsen in a minority of patients while on antidepressant treatment. Depression is associated with an increased risk of suicide-related events (such as suicidal thoughts, self-harm and attempted suicide) and an association between depression and obesity has been well-established previously.
Risk factors and risk groups	No at-risk groups or risk factors for suicidality were identified in the NB development programme due to the small number of events (n=4). A theoretical risk exists that obese patients have a higher risk of suicide as they have a higher risk of depression, which is a known risk factor for suicide. All antidepressants carry class SmPC statements for risk of suicide and suicidal behaviour. The NB clinical programme conducted a specific review for depression and suicidality, showing no impact of NB on risk of suicide and suicidal behaviour. Overall, the antidepressants class statements for this risk indicated it is predominantly established in paediatric, adolescent and young adult (≤ 24 years) patients with depression. However, based upon the ongoing evaluation of NB post-marketing data, the SmPC has been updated to clarify that suicidality events have been observed in NB treated patients of all ages. <u>Bupropion HCl historical experience</u> In the meta-analysis of bupropion HCl treated subjects by Wightman *et al.* the authors reported no differential treatment effects on suicidal ideation or behaviour, by gender or age regardless of treatment. However, the authors found that 18- to 24-year-old group had the greatest odds of having a suicide event. Risk factors for suicide among adult obese patients are unclear. In the *general population*, risk factors for suicide can include mental and addictive disorders, male gender, disrupted marital status, prior suicide attempt, reduced brain stem serotonergic activity, family history of psychiatric disorders or suicide, a firearm in the home, and recent severely stressful life event.
Risk minimisation measures	**Routine risk minimisation measures** The SmPC includes text regarding Suicide and suicidal behaviour in Section 4.4 (Special warnings and precautions for use) and section 4.8. The Package leaflet includes text regarding suicide in Section 2 and section 4. Mysimba is subject to medical prescription. **Additional risk minimisation measures** Physician educational kit, to reinforce indication and ensure appropriate patient selection, which contains: • SmPC • Physician Prescribing Checklist
Specific clinical measures	Close supervision of patients, particularly those at high risk and especially in early treatment and following dose changes. Monitoring for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour (SmPC section 4.4.)
Additional pharmacovigilance activities	NB-451 and NB-452

Important Potential Risk – OFF-LABEL USE AND ABUSE POTENTIAL	
Evidence for linking the risk to the medicine	There is a potential risk that Mysimba may be taken by other groups, since it is known that medicines to lose weight are sometimes wrongly

	taken by people (especially those with a history of anorexia or bulimia) who are of normal weight or below normal weight. There is also a risk that people who should not be prescribed Mysimba because they are at increased risk of side effects may be wrongly given the medicine.
Risk factors and risk groups	Risk factors for off-label use for NB (or for the individual components of NB) are based on the mechanism of action of both components. Substances acting on the reward system in the brain have a potential for drug abuse. Increasing evidence of the benefit of naltrexone's actions on opioid receptors with the potential of reactively increasing the production of endorphins and enkephalines in the patient's body and of naltrexone's actions on cell types such as the microglia with the potential of anti-inflammatory actions may predispose to NB use for indications different than the approved ones. Risk groups involve patients not properly educated about the mechanism of action and the correct dosing regimen of the NB combination product. Theoretically, subpopulations of subjects who may be at risk of off-label use of NB include those who have a BMI <27 kg/m2, those who are or overweight (e.g. 27 kg/m2 $\leqslant$ BMI <30 kg/m2) but who do not have predisposing risk factors; or individuals less than 18 years of age. Individuals who are bulimic or anorexic may seek off-label use of NB in search of a weight-loss product. Large doses of naltrexone can cause liver damage and are potentially fatal. Low doses given intermittently have the potential of mimicking endorphin effects. The re-uptake inhibitor bupropion is indicated for the treatment of depression. It is a monocyclic antidepressant that has been accidentally found to have potential effects on reducing nicotine addiction. It is structurally similar to stimulants such as amphetamine and inhibits dopamine and noradrenalin reuptake selectively. Off-label use of the combination product NB seems plausible for patients knowing about the anti-depressive action of the mono-component bupropion. Incorrect dosing may lead to bupropion overdose with an increased risk of cardiotoxicity, seizures and death. Bupropion HCl historical experience: No information was found in the literature regarding utilisation of bupropion HCl for the indication of weight loss by patients who would otherwise be considered off-label (e.g. patients with normal BMI). Naltrexone HCl historical experience: Documented examples of off-label use resulting from recreational use of naltrexone HCl have not been identified, and a literature search has not revealed evidence for diversion and overdose related to abuse of this drug. Naltrexone HCl does not produce euphoria, and, particularly at higher exposures, can produce dysphoria and gastrointestinal discomfort.
Risk minimisation measures	**Routine risk minimisation measures** The SmPC includes text regarding therapeutic indication in Section 4.1, correct use of NB in Section 4.2 (Posology and method of administration), contraindications (Section 4.3) and Special warnings and precautions for use (Section 4.4). The Package leaflet includes text regarding correct use of NB in Section 1, Section 2 and Section 3. Mysimba is subject to medical prescription. **Additional risk minimisation measures** Physician educational kit, to reinforce indication and ensure appropriate patient selection, which contains: • SmPC

	• Physician Prescribing Checklist
Additional pharmacovigilance activities	NB-451 and NB-452

Important Potential Risk – CONGENITAL MALFORMATIONS	
Evidence for linking the risk to the medicine	Product information for the bupropion monocomponent was recently updated to state that some epidemiological studies of pregnancy outcomes following maternal exposure to bupropion in the first trimester have reported an association with increased risk of certain congenital cardiovascular malformations specifically ventricular septal defects and left outflow tract heart defects. These findings are not consistent across studies. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.
Risk factors and risk groups	Risk groups or risk factors for congenital malformations could not be determined based on information from the NB clinical trials programme given the absence of cases.
Risk minimisation measures	**Routine risk minimisation measures** The SmPC includes text regarding pregnancy in Section 4.6 (Fertility, pregnancy and lactation) and Section 5.3 (Preclinical safety data). The Package leaflet includes text regarding pregnancy in Section 2. Mysimba is subject to medical prescription. **Additional risk minimisation measures** None

Missing information - USE DURING PREGNANCY	
Risk minimisation measures	**Routine risk minimisation measures** The SmPC includes text regarding use in pregnancy in Section 4.6 (Fertility, pregnancy and lactation) and Section 5.3 (Preclinical safety data). The Package leaflet includes text regarding pregnancy in Section 2. Mysimba is subject to medical prescription. **Additional risk minimisation measures** None

Missing information - DATA ON LONG-TERM / CHRONIC USE BEYOND 1 YEAR	
Risk minimisation measures	**Routine risk minimisation measures** SmPC states the need for continued treatment should be re-evaluated annually (Section 4.2). The package leaflet for NB states: Section 3 *After 16 weeks and each year after your treatment initiation, your doctor will evaluate whether you should continue to take Mysimba. Mysimba is subject to medical prescription.* **Additional risk minimisation measures** None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Study NB-CVOT study 2 is a condition of the marketing authorisation. The details of the study are under development in consultation with the applicable regulatory agencies; however, a very brief summary is presented below.

NB-CVOT study 2 – A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 4 Study to Assess the Effect of Naltrexone Extended Release (ER) /Bupropion ER on the Occurrence of Major Adverse Cardiovascular Events (MACE) in Overweight and Obese Subjects with Cardiovascular Disease

The purpose of the study is to determine the effects of NB relative to placebo on major adverse cardiovascular events (MACE) including cardiovascular death, non-fatal heart attack (myocardial infarction), and non-fatal stroke in overweight and obese subjects who are at a higher risk of having events because they have a history of cardiovascular disease with or without diabetes.

No post-authorisation efficacy studies have been conducted or are being planned.

II.C.2 Other studies in post-authorisation development plan

NB-451: An observational database study to identify real-world utilization patterns of Mysimba use among patients who are new users of Mysimba

This study will describe the utilization and safety of Mysimba in a real-world setting using electronic health records (EHR) and administrative health claims from European countries. Available characteristics of patients initiating Mysimba will be described, with particular focus on patients receiving Mysimba in a manner noncompliant with the SmPC at initiation, such as off label use or with a contraindication to the SmPC. This study also plans to evaluate the incidence of adverse events of special interest (AESI) in real-world settings.

NB-452: A cross-sectional survey to evaluate the effectiveness of the Mysimba® Physician Prescribing Checklist (PPC) among physicians in the European Union (EU)

This study will evaluate whether physicians prescribing NB have received, understood and complied with the Physician Prescribing Checklist as part of physician packet provided prior to drug supply. In addition, the study will summarize the specialty of the prescribing physicians.