08 November 2019
EMA/PRAC/613102/2015 Rev.2 accompanying GVP Module V Rev.2
Human Medicines Evaluation

EU Risk Management Plan for Mysimba (Naltrexone HCl/Bupropion HCl)

RMP version to be assessed as part of this application:

Data lock point for this RMP	23 October 2023
Version number	15.0
Date of final sign off	03 April 2025

Rationale for submitting an updated RMP:	Update of cardiovascular pharmacovigilance activities and risk minimisation measures: • Updated information for CVOT study as category 1 PASS (NB-CVOT-3, INFORMUS) • Updated risk minimisation measures
Summary of significant changes in this RMP:	Update RMP with details on CVOT study as category 1 PASS (NB-CVOT-3, INFORMUS) Risk minimisation measures: updates to Product Information and PPC with text on clinical measure of annual patient assessment; addition of Direct Healthcare Professional Communication (DHPC) as additional risk minimisation
Other RMP versions under evaluation	None

Details of the currently approved RMP:

RMP Version number	**Date of approval (opinion date)**	**Submitted within**
14.0	**28 November 2024**	EMEA/H/C/003687/II/0063 EMEA/H/C/PSUSA/00010366

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Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Naltrexone HCl/Bupropion HCl
Pharmacotherapeutic group(s) (ATC Code)	ATC Code: A08AA62 bupropion and naltrexone Group: A08AA Centrally acting antiobesity products
Marketing Authorisation Holder/Applicant	Orexigen Therapeutics Ireland Limited
Medicinal products to which this RMP refers	Naltrexone HCl/Bupropion HCl
Invented name(s) in the European Economic Area (EEA)	Mysimba **(also referred to as 'NB' for 'Naltrexone / Bupropion' in the remainder of the document)**
Marketing authorisation procedure	Centralised procedure under Article 3(2)(b) (Significant innovation or interest of patients at Community level)
Brief description of the product • chemical class • summary of mode of action important information about its composition	NB is a fixed-dose combination of naltrexone HCl and bupropion HCl. **Bupropion HCl** is a weak inhibitor of the neuronal biogenic amine reuptake (principally dopamine and norepinephrine). **Naltrexone HCl** is a mu-opioid receptor antagonist, of semi-synthetic origin. The exact neurochemical appetite suppressant effects of NB are not fully understood. The 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 receptor (MOP-R). Binding of β-endorphin to MOP-Rs 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.
Hyperlink to the Product Information	Mysimba® current Product Information

Indication(s) in the EEA Current (if applicable)	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 comorbidities (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.
Proposed (if applicable)	Not Applicable
Dosage in the EEA Current (if applicable)	Oral use. The maximum recommended daily dose of NB is two tablets taken twice daily for a total dose of 32 mg naltrexone hydrochloride and 360 mg bupropion hydrochloride. NB dosing is escalated over a 4-week period until achieving the total daily maintenance dose of 32 mg naltrexone HCl and 360 mg bupropion HCl.
Proposed (if applicable)	Not Applicable
Pharmaceutical form(s) and strengths Current (if applicable)	Naltrexone HCl 8 mg/Bupropion HCl 90 mg prolonged release tablets.
Proposed (if applicable)	Not Applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

List of Abbreviations	
ACE	Angiotensin Converting Enzyme
ADMET	Absorption, Distribution, Metabolism, Excretion and Toxicology
ADRs	Adverse Drug Reactions
AEs	Adverse Events
AELDMS	Adverse Events Leading to Discontinuation of Study Medication
AGEP	Acute Generalized Exanthematous Pustulosis
AHRQ	Agency for Healthcare Research and Quality
ALT/AST	Aspartate Aminotransferase / Alanine Aminotransferase
ANCOVA	Analysis of Co-Variance
ARBs	Angiotensin Receptor Blockers
BA	Bioavailability
BD	Bipolar Disorder
BE	Bioequivalence
BED	Binge Eating Disorder
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CAD	Coronary Artery Disease
CCB	Calcium Channel Blockers
CHD	Coronary Heart Disease
CHF	Cardiac Heart Failure
CHMP	Committee for Medicinal Products for Human Use
CV	Cardiovascular
CVD	Cardiovascular Disease
CVOT	Cardiovascular Outcome Trial
DA	Dopamine
DBP	Diastolic Blood Pressure
DHPC	Direct Healthcare Professional Communication
DMC	Data Monitoring Committee
DLP	Data Lock Point
DPP-4	Dipeptidyl Peptidase-4

List of Abbreviations	
DUS	Drug Utilisation Study
EASO	European Association for the Study of Obesity
ECGs	Electrocardiograms
EEA	European Economic Area
EHIS	European Health Interview Survey
EHR	Electronic Health Records
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GI	Gastrointestinal
GLP-1	Glucagon-like Peptide-1
GSK	GlaxoSmithKline
HCl	Hydrochloride
HDL	High-Density Lipoprotein
HF	Heart Failure
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A reductase
HRQo-L	Health-Related Quality of Life
ICH	International Conference on Harmonisation
ICSRs	Individual case safety reports
IL-6	Interleukin-6
IV	Intravenous
LDL	Low-Density Lipoprotein
LV	Left Ventricular
MACE	Major Adverse Cardiovascular Events
MAHs	Marketing Authorisation Holders
MAOI	Monoamine Oxidase Inhibitor
MEB	Medicines Evaluation Board
MHRA	Medicines and Healthcare products Regulatory Agency
MPA	Medical Products Agency
MRP	Mutual Recognition Procedure
NB	Naltrexone Hydrochloride / Bupropion Hydrochloride

List of Abbreviations	
NE	Norepinephrine
NEFA	Nonesterified Fatty Acid
NHANES	National Health and Nutrition Examination Survey
NNH	Number Needed to Harm
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
OA	Osteoarthritis
OSA	Obstructive Sleep Apnoea
PAI-1	Plasminogen Activator Inhibitor-1
PASS	Post Authorisation Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Pharmacodynamics
PET	Positron Emission Tomography
PhV	Pharmacovigilance
PL	Package leaflet
PIP	Paediatric Investigational Plan
PK	Pharmacokinetics
PK DDIs	Pharmacokinetic Drug-Drug Interactions
PRAC	Pharmacovigilance Risk Assessment Committee
PPC	Physician Prescribing Checklist
PT	Preferred Terms
QALYs	Quality-Adjusted Life Years
QWB	Quality of Well-Being Scale
RMP	Risk Management Plan
RMM	Risk Minimization Measures
RMS	Reference Member State
RR	Relative Risk
SAEs	Serious Adverse Events
SBP	Systolic Blood Pressure
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SNRIs	Serotonin–Norepinephrine Reuptake Inhibitors

List of Abbreviations	
SSRIs	Selective Serotonin Reuptake Inhibitors
TCAs	Tricyclic Antidepressants
TDM	Therapeutic Drug Monitoring
TME	Targeted Medical Event
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
WHO	World Health Organisation

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

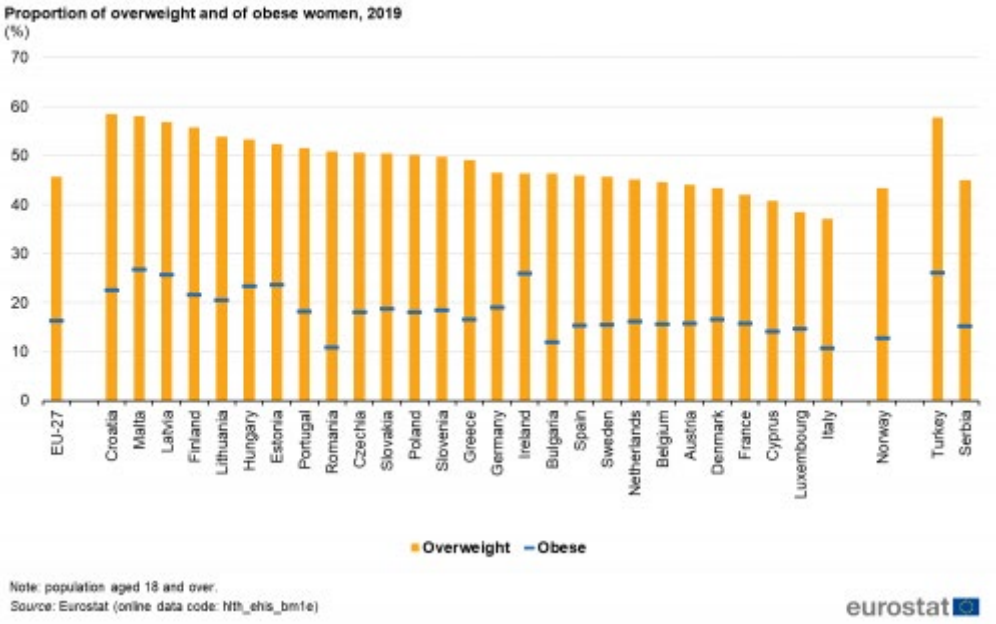
Indication- Obesity in Adults

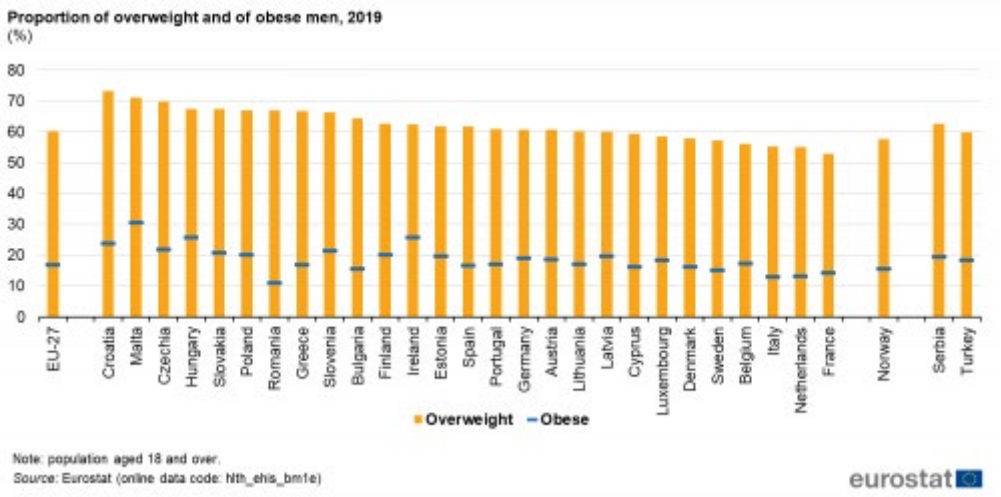
Incidence and Prevalence

In Europe, the European Commission's third wave of the European Health Interview Survey (EHIS), conducted between 2018 and 2020, reported that overall, the prevalence of overweight and obesity across countries is increasing at a rapid rate in most EU member states, with estimates of 52.7% of the adult (aged 18 and over) EU's population overweight in 2019. In the EU, the highest proportion of overweight adults in 2019 ranged between 37.1% in Italy and 58.5% in Croatia for women and between 52.9% in France and 73.2% in Croatia for men. According to the World Health Organization, worldwide obesity has nearly tripled since 1975. In 2016, 39% of adults aged 18 years and over were overweight and 13% were obese. It is anticipated that within the next 10 years, two out of every three persons will be overweight or obese in Europe (1). In the US, the National Health and Nutrition Examination Survey (NHANES) reported that in 2013-2014 70% of Americans were overweight or obese (2).

Obesity is a serious public health problem, as it significantly increases the risk of chronic diseases such as cardiovascular disease, type-2 diabetes, hypertension, coronary heart diseases and certain cancers. For specific individuals, obesity may further be linked to a wide range of psychological problems. For society as a whole, it has substantial direct and indirect costs that put a considerable strain on healthcare and social resources.

According to the World Health Organisation (WHO), Europe had the second highest proportion of overweight or obese people in 2014, behind the Americas. Globally, in 2014, 39% men and 40% of women aged 18 or over were overweight; overall, about 13% of the world's adult population (11% of men and 15% of women) were obese in 2016. This share rose above 58% in Europe and the Americas.





Obesity, age and gender

Eurostat, the statistical office of the European Union, reported a positive correlation between overweight/obesity, age and gender. In women, overall share of overweight population in 2019 was 45.7, and 60.2 for men. The prevalence (% of total population) of overweight/obesity was reported to be 25% amongst the 18-24 years old, with a systemic increase observed with age reaching up to 65.7% of the 65-74 years old overall share of overweight population in 2019 was 45.7, and 60.2 for men. In 25 of the 30 Member States that were part of the study, the largest share of overweight and obese men were from the 65-74 age group (3). Exceptions to this pattern were found in Denmark, Ireland, Sweden, Norway and Turkey, where the percentage of overweight was highest in the 54-64 age group.

In 2019, Eurostat released additional data. It found there to be no systematic difference in obesity levels between men and women; the proportion of obesity was higher for men in 17 of the Member States, and higher for women in 10 member states. In 2019, the highest proportion of obese men and women was recorded in Malta. Within a Member State however, significant gaps can be observed, with the proportion of obese men being much higher than that of women in Malta +3.9 percentage points – pp), Czech Republic and Luxembourg (3.8pp) presenting the highest differences and the percentage of obese women being much higher than that of men in Latvia (+6.1 pp), Estonia (+3.9 pp) and Lithuania (+3.5pp).

In nearly all Member States, the share of obesity increases with age. The widest gaps between the proportion of young people (aged 18-24) and older persons (aged 65-74) being obese were recorded in Czechia (76.4% for people aged 65 to 74 compared with 20.9% for those aged 18 to 24, or +56.4 pp). and Slovakia (+53.5), following by Croatia (+51.4), Greece (+51.3) and Latvia (+51.2). At EU level, a 40.7 percentage point gap is observed between young adults (25%) and older persons (65.7%) as regards obesity. About 1 young adult out of 5 is considered obese in Italy (18.0%), Lithuania (20.1%) Czechia (20.9%), and about 2 in 3 older persons in France (57.2%), and Denmark (57.6%).

Share of overweight population by sex and age, 2019
(%)

	Males	Females	Total						
	18 years or over		18 years or over	18 to 24	25 to 34	35 to 44	45 to 64	65 to 74	75 years or over
EU	60.2	45.7	52.7	25.0	39.3	49.7	59.8	65.7	59.3
Belgium	56.2	44.6	50.2	26.2	36.2	49.0	57.3	62.6	52.7
Bulgaria	64.3	46.3	54.9	23.2	37.2	48.8	63.4	70.2	62.6
Czechia	69.8	50.6	60.0	20.9	43.3	57.8	68.7	76.4	67.8
Denmark	57.8	43.3	50.4	26.0	40.0	50.1	59.6	57.6	50.5
Germany	60.7	46.5	53.5	28.2	40.8	52.3	60.0	66.1	57.4
Estonia	61.7	52.3	56.7	26.5	35.9	51.5	67.0	75.7	67.8
Ireland	62.3	46.4	54.4	39.7	52.1	52.9	61.5	59.7	57.5
Greece	66.8	49.1	57.6	23.4	39.7	50.4	66.0	74.7	68.8
Spain	61.7	45.9	53.7	25.1	37.4	49.6	60.4	68.3	66.0
France	52.9	42.0	47.2	22.3	37.8	43.7	53.9	57.2	53.6
Croatia	73.2	58.5	64.8	27.3	45.1	59.8	69.3	78.7	70.0
Italy	55.3	37.1	45.7	18.0	31.2	39.7	49.9	58.8	55.0
Cyprus	59.4	40.8	49.8	23.5	32.7	49.2	61.6	65.7	64.7
Latvia	60.1	56.9	58.3	22.3	38.9	52.4	67.8	73.5	71.7
Lithuania	60.2	53.9	56.8	20.1	40.0	48.2	69.1	74.0	65.5
Luxembourg	58.5	38.4	48.4	24.1	36.5	46.7	56.9	62.5	57.1
Hungary	67.3	53.3	59.9	31.3	43.9	55.4	68.4	76.4	67.3
Malta	71.0	58.0	64.8	38.6	56.6	66.1	73.3	73.7	72.5
Netherlands	55.1	45.1	50.0	25.0	39.4	49.8	57.4	60.2	54.3
Austria	60.6	44.1	52.2	27.2	39.0	48.3	59.9	66.4	58.7
Poland	66.9	50.2	58.1	26.6	43.4	55.3	67.8	73.7	65.4
Portugal	60.9	51.5	55.9	27.6	38.9	52.3	62.9	70.4	63.6
Romania	66.9	50.9	58.7	25.4	42.8	55.4	70.2	72.3	62.3
Slovenia	66.3	49.8	58.1	26.1	42.7	53.3	66.1	72.9	68.8
Slovakia	67.3	50.5	58.7	23.8	42.0	58.0	68.3	77.3	73.0
Finland	62.5	55.8	59.0	30.4	45.9	58.9	65.9	69.1	65.7
Sweden	57.1	45.7	51.3	27.5	39.7	50.3	60.9	60.1	52.4
Norway	57.7	43.3	50.6	28.2	40.8	50.9	61.0	57.6	49.2
Serbia	62.7	45.0	53.6	24.1	42.1	51.8	62.4	65.1	53.8
Turkey	59.8	57.8	58.8	26.9	44.8	65.1	74.3	73.3	59.8

Source: Eurostat (online data code: hlth_ehis_bm1e)

eurostat

Source of graphic: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=File:Share_of_overweight_population_by_sex_and_age,_2019_(%25).png

Obesity across Europe
The prevalence of obesity in Europe varies across the region (3). The lowest prevalence of obesity was observed in Romania (10.8% for women and 11.1% for men), Italy (10.7% and 12.9%), Bulgaria (11.9% for women), and France (14.3% for men); whereas the highest prevalence for women was observed in Estonia (23.6%), Latvia (25.7%), Ireland (26.0%) and Malta (26.7%). For obese men, the highest prevalence was found in Croatia (23.7%), Ireland (25.7 %), Hungary (25.8%) and Malta (30.6%).

Obesity and ethnicity
Ethnicity is associated with a range of different body shapes and different physiological responses to fat storage. Body mass index (BMI) thresholds for defining obesity can be significantly lower in non-European populations regarding obesity related morbidity and mortality. In the UK, the most reliable figures of obesity prevalence across ethnic groups come from the National Health Service report in 2004 (4). The distribution of obesity (BMI ≥ 30 kg/m^2) in men ranged between 6% among individuals of Bangladeshi and Chinese origin to 25% among Irish and Black Caribbean populations. In women, the prevalence of obesity ranged between 8% among individuals of Chinese origin to 38% among Black Africans.

Obesity and Education level
The proportion of women who were overweight was lower among those with higher levels of educational attainment, this pattern was consistent among all EU member states. The difference in overweight women with a tertiary education and those with no more than a lower secondary education was at least 32 pp in Portugal (32.0 pp), Greece (32.6pp) and France (34.7 pp) [1].
For men, there was no clear pattern linking educational attainment levels and being overweight. The differences in the proportion of men who were overweight according to educational attainment were generally smaller than for women. In 13 EU Member States, the highest proportion of men who were overweight was recorded among those with no more than a lower secondary level of educational

attainment, while only in 2 countries - Estonia and Latvia - the highest proportion of overweight men was recorded among those with a tertiary level of education.

Risk factors for Obesity

Risk factors for obesity are complex and multifactorial (5). Complex interactions between biological (including genetic and epigenetic), behavioural, social and environmental factors (including chronic stress) are involved in regulation of energy balance and fat stores.

Main Treatment Options for Obesity

Lifestyle modification, where lower-energy diets are combined with increased physical activity and behavioural therapy has been the cornerstone of treatment for obesity.

Few pharmacological obesity treatment options have been available in Europe in the last decade. These include Xenical® (orlistat), which is currently available by prescription only, over the counter (Alli®); Acomplia® (rimonabant), which was available until October 2008 when the marketing authorisation was suspended (and withdrawn in January 2009); and sibutramine (marketed under various trade names) until January 2010 when the marketing authorisation was suspended. Currently, orlistat and Saxenda® (liraglutide) are the only other pharmacological treatment options in Europe.

More invasive options (e.g. gastric banding, bariatric surgery) do result in greater weight loss than is achievable with pharmacotherapy, however these options are targeted primarily to those patients with the higher BMIs (generally BMI >40 kg/m2) and/or patients with significant comorbidities (e.g., patients with BMI >35 kg/m2 with type 2 diabetes) because of the risks of surgery and capacity limitations in most EU countries.

Mortality and Morbidity (natural history)

The WHO estimates that 1 out of every 13 deaths in the EU is likely to be related to excess weight which translates to more than 1 million deaths in the WHO European region each year (6). Obese subjects (BMI>30 kg/m^2) have been reported to experience greater mortality than normal weight or overweight subjects. Morbidity and mortality were found to be markedly influenced by the patient's age, gender, ethnic origin, and social status (7). A recent meta-analysis indicated that after adjusting for potentially confounding factors, obese individuals with a BMI ≥ 35 kg/m^2 had a 29% greater risk of mortality (RR=1.29, 95% CI, 1.18-1.41) compared to those who were normal weight (8). A large prospective cohort study in an older population (50-71 years old) revealed that individuals in the highest (and lowest) BMI categories experienced the highest risk of death. The results were consistent across all racial groups and ages (9).

Overweight and obesity contribute to 80% of cases of type 2 diabetes, 35% of ischaemic heart disease and 55% of hypertensive disease among adults in Europe (6). Moreover, obesity has also been shown to be associated with a wide range of other adverse outcomes including stroke, gallbladder disease, osteoarthritis, sleep apnoea, respiratory problems, some types of cancer (endometrial, breast, prostate, and colon), complications of pregnancy, menstrual irregularities, hirsutism, stress incontinence, and psychological disorders (depression, anxiety) (10).

Overweight and obese subjects show significantly reduced physical and mental quality of life scores compared with individuals with a normal BMI (11)(12).

The body mass index (BMI) is the most practical way to evaluate the degree of overweight. It is calculated from the height and weight as follows: BMI = body weight (in kg) ÷ square of stature (height, in meters). The recommended classifications for BMI adopted by the National Heart, Lung, and Blood Institute and the World Health Organization (WHO), and affirmed in the American Heart Association (AHA)/American College of Cardiology (ACC)/The Obesity Society (TOS) Guidelines are: Normal weight: BMI ≥ 18.5 to 24.9 kg/m^2; Overweight: BMI ≥ 25 to 29.9 kg/m2; Obesity: BMI ≥ 30 kg/m^2; Severe obesity: BMI ≥ 40 kg/m^2 (or ≥ 35 kg/m^2 in the presence of comorbidities).

Healthy" obese adults may be unable to maintain their metabolically healthy profile over time, according to a study published Jan. 5, 2015 in the Journal of the American College of Cardiology (ACC News Story: What is the Natural Course of Healthy Obesity over 20 years?).

Using data from the Whitehall II cohort study of British government workers, researchers from the Department of Epidemiology and Public Health at University College London in England sought to examine the natural course of healthy obesity – defined as a lack of metabolic risk factor clustering in obesity – over two decades. Of the 2,521 participants ages 39 to 62 years old (75 percent male), 66 were healthy obese adults at baseline (measured in 1992 or 1994). While obese patients were defined as those with a body mass index as ≥ 30kg/m2, metabolically healthy patients were those with less than two of the following: high-density lipoprotein cholesterol level <1.03 mmol/l (men) and <1.29 mmol/l (women); blood pressure ≥ 130/85 mm Hg or use of antihypertensive medication; fasting plasma glucose level ≥ 5.6 mmol/l or use of antidiabetic medication; triacylglycerol level ≥ 1.7 mmol/l; and homeostatic model assessment of insulin resistance less than 2.87.

Researchers analysed participants in the cohort study with data collected on obesity and metabolic status at baseline and follow-up examinations every five years. The results showed that after five years, 32 percent of healthy obese participants were re-categorized as unhealthy obese. After 20 years (2012/2014), 52 percent of healthy obese at baseline were unhealthy obese, with only 10 percent measured at healthy non-obese. The study further shows that healthy obese adults were "eight times more likely to progress to an unhealthy obese state after 20 years than healthy non-obese adults."

The authors note that the "natural course of healthy obesity is progression to metabolic deterioration." Lead study author, Joshua Bell, MSc, remarked, "healthy obese adults show a greater risk for developing cardiovascular disease than healthy normal-weight adults, although this risk is not as great as for the unhealthy obese... Healthy obesity is only valid if it is stable over time, and our results indicate that it is often just a phase. All types of obesity warrant treatment, even those which appear to be healthy. And as we now see, healthy obese adults tend to become unhealthy obese over time, providing further evidence against the idea that obesity can be healthy."

Important co-morbidities:

Obesity contributes to a wide-ranging set of comorbid conditions, the most significant among adults in Europe include type 2 diabetes, ischaemic heart disease and hypertensive disease (6). Obesity also increases mortality from a number of cancers (23). There is an association of obesity with dyslipidaemia, sleep apnoea, arthritis, hyperuricaemia, gall bladder disease, heart failure, cardiac arrhythmia, stroke, erectile dysfunction and menstrual irregularities (24). Psychological disorders including depression, anxiety, low self-esteem, seasonal affective disorder, sleep deprivation, eating disorders including binge eating, bulimia nervosa and anorexia nervosa are important co-morbidities found in the target population.

Obesity, Dyslipidaemia, Coronary Heart Disease (CHD) and Cardiovascular Disease
Overweight, obesity, and excess abdominal fat have been shown to be directly related to cardiovascular risk factors, including elevated total cholesterol, low-density lipoprotein (LDL)-cholesterol, triglycerides, blood pressure, and decreased high-density lipoprotein (HDL)-cholesterol in both men and women and across age groups, with a consequent increased risk of CHD, as shown by long-term epidemiologic data (25). There is an increase in the prevalence of dyslipidaemia from 8.9% for normal weight to 19.0% for a BMI ≥40.0 kg/m^2 (26).

Excess body weight is thought to account for up to one quarter of cases of hypertension in adults (23). The age-adjusted relative risk (RR) for new hypertension is highly associated with overweight status (men: RR, 1.46; women: RR, 1.75) (27). With increasing overweight and obesity class, there is an increase in the prevalence of hypertension (18.1% for normal weight to 52.3% for BMI ≥40.0 kg/m^2).

Recent studies have shown that the risks of non-fatal myocardial infarction and CHD death increase with increasing BMI (10). Subjects with visceral (android/abdominal) obesity represent a subgroup of obese individuals with the highest risk for cardiovascular disease, stroke and transient ischaemic attacks and are also at greater risk of metabolic complications when compared to those with lower body (gynoid) obesity. In addition, risks are lowest in men and women with BMIs of 22 kg/m^2 or less and increase with even modest elevations of BMI (28). One in three fatal and one in seven non-fatal cardiovascular disease CVD cases are attributable to overweight and obesity (29). Heart failure is markedly increased in obese patients (30).

Obesity and Diabetes
Prospective studies have shown an increased risk of diabetes with increased body weight, in all ethnic groups. The development of type 2 diabetes has been found to be associated with weight gain after age 18 in both men and women. In a prospective study conducted in the US, it was estimated that 27% of new cases of diabetes was attributable to weight gain of 5 kg (11 pounds) or more in adulthood (31).

There is an increase in the prevalence of diabetes from 2.4% for normal weight to 14.2% for a BMI ≥40.0 kg/m^2. With normal weight individuals as a reference, individuals with BMI ≥40.0 kg/m^2 had an adjusted odds ratio of 5.1 (95% CI 3.7 to 7.0) for diabetes (26).

Obesity and Psychological Disorders
An important association exists between obesity and psychiatric disorders. Obesity and depression are increasingly prevalent and comorbid, with a bidirectional relationship. Increasing adiposity in obese women has been significantly negatively associated with quality of life, with an increase of 1 BMI unit associated with decreases of 1.62 in self-esteem; the prevalence of symptoms of anxiety (70.3%) and depression (66.2%) was consistently high (32). The observed relationship is more consistent in women than in men and is stronger in more severely obese individuals.

Obesity has prognostic implications as a comorbidity in individuals with bipolar disorder (BD). The relationship between obesity and BD is seen as alterations in the structure and function of the central nervous system, greater recurrence of depression, cognitive dysfunction and risk of suicidality (33).

Obesity and Cancers
A large body of epidemiological evidence links obesity to increased cancer incidence, with some studies also indicating poorer survival in obese patients with cancer (34) (35) (36). Relative risks associated with overweight and obesity have been reported for colon cancer and breast cancer in postmenopausal women (less than 2.0), for uterine cancer (2 to 10), kidney cancer (1.5 to 4), adenocarcinoma of the oesophagus (2 to 3), gallbladder cancer in women (about 2), pancreatic cancer (about 2), ovarian cancer (1.5 to 2.0 for the highest body-mass-index categories), as well as for liver cancer (2.0 to 4.0). In men, the relative risks of death from all cancers, compared with men of normal weight, were 1.20 (95 percent CI, 1.08 to 1.34) in men with BMI 35.0-39.9 and 1.52 (95 percent CI, 1.13 to 2.05) in men with BMI of at least 40.0. Results for the total population of women were similar. Significant positive linear trends in death rates are observed with increasing BMI for all cancers, oesophageal cancer, stomach cancer, colorectal cancer, liver cancer, gallbladder cancer, pancreatic cancer, prostate cancer, kidney cancer, non-Hodgkin's lymphoma, multiple myeloma, and leukaemia in men; colorectal cancer, liver cancer, gallbladder cancer, pancreatic cancer, breast cancer, cancer of the corpus and uterus, not otherwise specified, cervical cancer, ovarian cancer, kidney cancer, non-Hodgkin's lymphoma, multiple myeloma, and "other" cancers in women.

Obesity and Kidney Diseases
Kidney diseases, microalbuminuria, proteinuria, hyperfiltration, and impaired renal function have been shown to be associated with obesity. Obesity can be a risk factor for chronic kidney disease irrespective of the presence/absence of diabetes, arterial hypertension, and other comorbidities (37).

Obesity and Osteoarthritis
Obesity increases the risk of knee OA by a variety of mechanisms, such as increased joint loading and changes in body composition and behavioural factors, including diminished physical activity and subsequent loss of protective muscle strength (38).

Obesity, Lung Function and Sleep Disturbances
Obese individuals often present a restrictive respiratory pattern i.e., a reduction in lung volume and capacity as compared to healthy individuals. Obesity predisposes to obstructive sleep apnoea (OSA). Intermittent hypoxia exacerbates the metabolic dysfunction and the cardiometabolic risk (39).

Part II: Module SII - Non-clinical part of the safety specification

Key Safety findings (from non-clinical studies)	**Relevance to human usage**
Toxicity	

Key Safety findings (from non-clinical studies)	Relevance to human usage
Single and repeat-dose toxicity There has been no clear evidence of target organ toxicity for naltrexone HCl or bupropion HCl in any species. *Naltrexone HCl* Clinical signs including mild excitation, hyperirritability, tremor, and salivation at high repeat doses, but without evidence of any other significant toxicological effects related to naltrexone HCl. *Bupropion HCl* Clinical signs were found at high doses indicating effects on the central nervous system, gastrointestinal system and genitourinary system. However, no evidence of histopathological effects in these organ systems was reported. Reproductive/ Developmental toxicity The current developmental and reproductive toxicity programmes for naltrexone HCl and bupropion HCl mono-components, indicate a relatively low risk to humans. There was no evidence of teratogenicity in rats or rabbits.	Systemic exposures of patients to the individual drugs are fully covered by the existing non-clinical data. Non-clinical data reveals no special hazard for humans based on conventional studies of safety, pharmacology, and repeat dose toxicity (NB SmPC Section 5.3). The lack of teratogenicity from the animal studies is augmented by widespread use post-authorisation of the single components. However, NB should not be used during pregnancy and breastfeeding (NB SmPC Section 4.6). No reproductive toxicity studies on the combination product were required further to the European guideline on the non-clinical development of fixed combinations of medicinal products (EMEA/CHMP/SWP/258498/2005).
Nephrotoxicity *Naltrexone HCl* No toxicologically significant findings have been observed apart from excess urination in rats in reproduction studies. *Bupropion HCl* There were statistically significant increases in relative kidney weights of rats in a 55-week study at 100 mg/kg/day.	Information on nephrotoxicity has been limited in the NB clinical development programme. Though NB has not been extensively evaluated in subjects with renal insufficiency in the completed studies of the clinical development programme, a substantial proportion of subjects in the cardiovascular outcomes trial Study NB-CVOT (27%; n=2394, placebo n=1174; NB n=1220) exhibited mild or moderate renal impairment (eGFR 30 to 90 mL/min) at screening; 15% of these subjects were classified as having moderate renal impairment (n=348; eGFR 30-59 mL/min). Based on data from these subjects, the safety profile of patients with mild renal failure has been characterized and is shown to be similar to that for patients without 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). 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. (NB SmPC Section 4.2).

Key Safety findings (from non-clinical studies)	**Relevance to human usage**
Hepatotoxicity *Naltrexone HCl* Given alone, naltrexone HCl (200 mg/kg, SC) has no effect on hepatic glutathione; however, it blocked the decreases induced by both opioids. *Bupropion HCl* In a 52-week study, dogs were administered 40, 80, or 150 mg/kg/day bupropion HCl. Hepatic changes were noted in the histopathological examination at all doses at 26 weeks, but only at 80 and 150 mg/kg/day at 52 weeks. These changes were minimal and included centrilobular hepatocellular vacuolation, very slight intrahepatic bile duct proliferation, slight centrilobular fibroplasia, and slight Kupffer cell proliferations. These histopathological changes were not evident in dogs after a 2-month recovery period.	Information on hepatotoxicity has been limited in the NB clinical development programme. At recommended doses in humans, bupropion HCl is primarily metabolised by the cytochrome P450 isozymes. This suggests that the hepatic findings in laboratory animals have only limited importance in the evaluation and risk assessment of bupropion HCl (40). There has been a single pharmacokinetic clinical trial completed in which NB has been evaluated in subjects with hepatic impairment. (NB SmPC Section 4.4). NB is contraindicated in severe hepatic impairment and is not recommended in patients with moderate hepatic impairment. 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) (NB SmPC Section 4.2).
Genotoxicity/ Carcinogenicity The genotoxicity and carcinogenicity of naltrexone HCl and bupropion HCl have been comprehensively tested. *Bupropion HCl* Genotoxicity data indicate that bupropion HCl is a weak bacterial mutagen, but not a mammalian mutagen, and therefore is of no concern as a human genotoxic agent. Bupropion HCl did not produce increase in malignant tumours in mice or rats. *Naltrexone HCl* 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.	The active components of NB are not considered to present a carcinogenic risk, based on the available data. Conventional genotoxicity studies revealed no specific hazard of naltrexone HCl for humans.

Key Safety findings (from non-clinical studies)	**Relevance to human usage**
General safety pharmacology	
Cardiovascular *Bupropion HCl* Bupropion HCl has been shown to decrease the sinus rate and shorten the action potential duration at high concentrations in isolated tissue but has no significant effects on cardiovascular function in anesthetised dogs. *Naltrexone HCl* In rats, naltrexone HCl was shown to have no effect on heart rate or arterial blood pressure after repeated dosing. In rabbits and dogs, decrease in heart rate was observed but no other effects on haemodynamic parameters were noted. Acute dosing in squirrel monkeys had only modest effects on blood pressure.	The safety of both agents is fully characterised and the safety and tolerability profile of NB in clinical studies has been reported to be consistent with that of the mono-components. Blood pressure and pulse should be measured prior to initiation of therapy with NB and should be assessed at regular intervals consistent with usual clinical practice. If patients experience clinically relevant and sustained increase in blood pressure or pulse rate because of NB treatment, it should be discontinued. Treatment with Mysimba should be discontinued if there are concerns with the safety or tolerability of ongoing treatment, including concerns about increased blood pressure (NB SmPC section 4.4). Naltrexone / bupropion should be given with caution to those patients with controlled hypertension and must not be given to patients with uncontrolled hypertension (NB SmPC Section 4.4). NB 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 (NB SmPC Section 4.4). A cardiovascular outcomes trial (Study NB-CVOT) involving 8,905 patients (4,455 randomized to NB and 4,450 to Placebo) was conducted to further evaluate the CV effects of treatment with NB by demonstrating that the occurrence of MACE (CV death, nonfatal MI, nonfatal stroke) with NB versus placebo does not adversely affect the benefit-risk profile of the combination therapy, and more specifically, in the target population of overweight and obese subjects already at increased risk of adverse CV outcomes. The last prespecified analysis performed prior to the early termination of the study was performed using 207 accrued MACE from 192 subjects. In the NB group, 90 subjects (2.0%) experienced a primary MACE, compared with 102 (2.3%) in the placebo group (HR 0.88; adjusted CI: 0.57, 1.34). Similarly, the final analysis was performed based on full totality of the data using 264 accrued MACE from 243 subjects. In the NB group, 119 subjects (2.7%) experienced a primary MACE, compared with 124 (2.8%) in the placebo group (HR 0.95; adjusted CI: 0.65, 1.38). These data demonstrate that the risk of MACE is not increased in overweight and obese patients at risk for adverse CV outcomes.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Nervous system Convulsions were observed at high doses in a single-dose toxicity study of bupropion HCl in mice. A single-dose, 26-week, carcinogenicity study was performed in CD (SD) BR rats in which bupropion HCl 100, 200 or 300 mg/kg/day was administered. Intermittent convulsions have been reported almost exclusively at a dose of 300 mg/kg/day. Convulsions were also reported during a 52-week repeat-dose toxicity study in dogs at a dose of 150 mg/kg/day and in a reproductive toxicity study in rabbits (maternal in the teratology evaluation) at a dose of 100 and 150 mg/kg/day. The reported doses causing convulsions largely exceed the proposed commercial dose for NB.	Data from bupropion HCl product information and the literature indicate that bupropion HCl is associated with a dose-related risk of seizures (41). For up to 300 mg/day of Wellbutrin SR, 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. The C_{max} of bupropion HCl in the NB product is similar to that of commercially available bupropion HCl doses of 300 mg/day. The rate of seizure in the NB clinical programme was consistent at <0.1%. NB should not be used in patients with a current seizure disorder or a history of seizures. (NB SmPC Section 4.3). NB should be discontinued and not restarted in patients who experience a seizure while being treated with the medicinal product (NB SmPC Section 4.4).
Mechanisms for drug interactions In vitro studies have confirmed that naltrexone HCl does not have the potential to inhibit or induce cytochrome P450 (CYP) enzymes and has no known PK drug-drug interactions (aside from changes attributed to the effect of food) (42,43). Co-administration of NB with drugs that are metabolised by the CYP2D6 isozyme can increase the PK concentrations of CYP2D6 substrates by non-competitive inhibition (44–46). PK interactions between both mono-components have been assessed during a human PK interaction study and have been ruled out. Refer to Part II Module SVII for further details on mechanisms for drug interactions.	Pharmacokinetic and pharmacodynamics drug interactions based on clinical data or assumptions are provided in Part II Module SVII.
Other toxicity-related information or data	
None	

Conclusion on non-clinical data:

Both naltrexone HCl and bupropion HCl have been used individually in humans for more than 37 and 22 years in EU, respectively. The pharmacology, pharmacodynamics, absorption, distribution, metabolism, excretion and toxicology (ADMET) of each molecule has been characterised sufficiently (in both animals and humans) to the extent that it can now be predicted that neither would interfere with the ADMET of the other molecule.

There is no potential for toxicological interactions/potentiating effect and the pharmacokinetic profile and clinical data on the combination showed a safety profile similar to that of the individual components already approved. As existing public domain, non-clinical data is available to assess the safety of naltrexone HCl and bupropion HCl, it was thought unnecessary to assess the non-clinical safety pharmacology or toxicology of prolonged release fixed combination naltrexone HCl and bupropion HCl formulation in animals, in line with EMEA/CHMP/SWP/258498/2005 guideline on the non-clinical development of fixed combinations of medicinal products.

The pharmacokinetic, pharmacodynamic, and safety data from clinical studies supports the conclusions drawn from the analysis of existing nonclinical public domain data.

Part II: Module SIII - Clinical trial exposure

Brief overview of development

Naltrexone HCl

Naltrexone HCl has been approved in EU member states from 1984 (47) for the treatment of opioid addiction and for alcohol addiction since 1996. According to Bristol-Myers Squibb, marketing authorisations for the originator Nalorex® are currently held in the following EEA countries: Belgium, Finland, France, Germany, Greece, Ireland, Luxembourg, the Netherlands, Portugal, Spain and UK. Since its initial approval, generic products have been made available in the EU (Naltrexone HCl Accord: Belgium, Denmark, Estonia, Finland, Germany, Ireland, Italy, Latvia, Lithuania, The Netherlands, Norway, Poland, Portugal, Spain, and UK; Naltrexone HCl POA: Denmark, Finland, Norway, and Sweden).

Bupropion HCl

In 1999, bupropion HCl prolonged-release tablets were approved (under the trade name Zyban®) through the Mutual Recognition Procedure (MRP) as an aid for use in *smoking cessation* where the Netherlands acted as the Reference Member State (RMS). Zyban® has been authorised with a recommended starting dosage regimen of 150 mg daily increasing to 150 mg twice daily after Day 6 of treatment. Bupropion HCl as an 'aid to smoking-cessation in combination with motivational support in nicotine-dependent patients' is authorised in the Member States of the European Economic Area (EEA) under the following names:

- *Zyban*®: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Norway, Portugal, Sweden, the Netherlands and the UK
- *Quomem*®: Austria, Spain, and the Netherlands
- *Zyntabac*®: Spain, and the Netherlands
- *Geronplase*®: Spain

For the treatment of *major depressive episodes*, bupropion hydrochloride in its prolonged-release tablet formulation was approved in 2007 through the MRP procedure in the EU under the trade name Wellbutrin® XR (the Netherlands acted as RMS). Marketing authorisation was granted on 10 January 2007 for two dosage strengths (150 mg and 300 mg, to be taken once daily) and has recently been the subject of a completed MRP renewal in November 2010. The application was made as a full application under Article 8(3) for a known active substance. Specific comments were made with respect to the recommended dosage of 300 mg a day based upon the reference to bupropion HCl immediate release product Zyban®. The Public Assessment Report [NL/H/785/01-02/DC] issued by the Medicines Evaluation Board (MEB) contains comments concerning the dose-response relationship for the extended release formulation of bupropion HCl.

This medicinal product is authorised in the Member States of the EEA under the following trade names:

- *Wellbutrin*® XR: Austria, Belgium, Luxembourg, Cyprus, Greece, Italy, Malta, Poland, Portugal, Slovenia, Switzerland, and the Netherlands.
- *Elontril*®: Austria, Czech Republic, Estonia, Germany, Hungary, Iceland, Latvia, Lithuania, Portugal, Romania, Slovakia, Spain and the Netherlands
- *Magerion*®: Germany and Sweden
- *Wellbutrin*® Retard: Norway
- *Voxra*®: Finland and Sweden

On 19 February 2002, Germany triggered a referral to the European Medicines Agency (EMA) under Article 36 of Directive 2001/83/EC [EMA/CPMP/27610/02] and requested that the Committee for Medicinal Products for Human Use (CHMP) provide an opinion on whether the marketing authorisations of bupropion HCl-containing products indicated as an 'aid to smoking cessation in combination with motivational support in nicotine-dependent patients' should be maintained, changed, or withdrawn, based on reported serious suspected adverse reactions (i.e. depression, suicidal ideation, suicide, seizures, undesirable cardiovascular effects, and angioedema).

Written explanation was provided by the Marketing Authorisation Holders (MAHs) on 21 May 2002 which reported that the immediate-release formulations of bupropion HCl were associated with a seizure incidence of approximately 0.4% in patients treated at dose range of 300 to 450 mg/day. However, at doses of Wellbutrin SR 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 of 400 mg/day. Therefore, the prolonged-release formulations of bupropion HCl appear to be associated with a lower risk of seizure compared to the immediate-release formulation. Based on re-evaluation of these data, CHMP concluded that the benefit/risk balance of bupropion HCl-containing medicinal products remains favourable for the current indication and adopted an opinion on 25 July 2002 recommending the maintenance of the Marketing Authorisations with amendments to the Summary of Product Characteristic (SmPC). The CHMP also recommended that bupropion HCl should be used in accordance with smoking cessation guidelines [EMA/CPMP/27610/02].

Naltrexone HCl/Bupropion HCl (NB)

The clinical development of NB has been discussed through Scientific Advice meetings with the Swedish Medical Products Agency (MPA), the UK Medicines and Healthcare Products Regulatory Agency (MHRA), and the Dutch Medicines Evaluation Board (MEB) between April and May 2012. No Scientific Advice meeting was held with the CHMP.

The NB clinical development programme is composed of 24 completed trials, including 15 Phase 1, five Phase 2, and four pivotal Phase 3 studies. Across the Phase 2 and 3 studies, a total of 3473 subjects have been exposed to NB for a total of 2313 patient-years, including 2694 who received the 32 mg naltrexone HCl and either 360 mg (the intended dose to be marketed) or 400 mg bupropion HCl PR. In addition, a Phase 2 study NB-431 (a functional magnetic resonance imaging (MRI) brain function study which enrolled 46 subjects) and studies NB-CVOT (a cardiovascular outcome trial) and NB-404 have not been incorporated as part of the integrated exposure and safety analyses.

The Phase 1 programme consisted of the following 15 studies:

- Comparative bioavailability/bioequivalence (BA/BE) (Studies NB-221, NB-225, NB-228, NB-229, and NB-230)
- Evaluation of the effect of food on the PK of NB (Studies NB-233, NB-236, NB-237, and NB-239)
- Potential of pharmacokinetic drug-drug interactions (PK DDIs) between NB tablets and representative medications from pharmacological classes likely to be prescribed in parallel with NB (Studies NB-232, NB-233, NB-234, and NB-236)
- The PK of a new formulation of NB (combination monolayer tablets) that is not currently under review (NB-231, NB-237, NB-238 and NB-239)

The Phase 2 programme consisted of five completed studies, as summarised below:

- Two studies (OT-101 [24-week proof of concept] and NB-201 [24 weeks of double-blind treatment with a 24-week extension]).
- Two open-label studies were completed in special populations of overweight and obese subjects (i.e. nicotine-dependent subjects [NB-401] and subjects who had major depression [NB-402]).
- One study (NB-431) was completed which used functional MRI imaging methods to assess the effects of NB on the brain's response to food cues.

The Phase 3 programme included four pivotal, 56-week, multicentre, randomised, double-blind, placebo controlled studies (Studies NB301, NB302, NB303, and NB304) in obese and overweight subjects.

To supplement the results of the completed trials, a large cardiovascular outcome trial (NB-CVOT; the Light Study) was conducted to support marketing authorisation, at the US Food and Drug Administration's (FDA) request, to address the theoretical risk of adverse cardiovascular outcomes as a result of the minor increase in blood pressure observed in Phase 3 trials with the product. Study NB-CVOT was a multicentre, randomised, double-blind, placebo-controlled study assessing the

occurrence of Major Adverse Cardiovascular Events (MACE; defined as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in overweight and obese subjects with cardiovascular risk factors receiving NB. In addition, the single dose pharmacokinetic studies NB-1005 and NB-1006 provided data on the use of the product in populations with varying degrees of hepatic and renal dysfunction (respectively).

Unless otherwise specified, 'NB clinical trials programme' throughout this document encompasses Phase 1, Phase 2 clinical trials with NB as well as NB-301, NB-302, NB-303 and NB-304 Phase 3 studies.

Clinical trial exposure

As stated above, the clinical trial exposure from the 'NB clinical trials programme' presented in the following tables include the Phase 1, Phase 2 clinical trials with NB as well as NB-301, NB-302, NB-303, and NB-304 Phase 3 studies. This is the patient population on which the Integrated Summary of Safety was comprised and has supported the worldwide registration of the product.

NB clinical trials programme

Table SIII.1: Duration of exposure (by indication)

Indication: Obesity	PLACEBO (n=1515) n (%)		NB (n=3239) n (%)	
Duration of exposure (at least)	Persons	Person time in years	Persons	Person time in years
≥ 1 day to < 4 weeks	76 (5.0%)		427 (13.2%)	
≥ 4 weeks to < 8 weeks	126 (8.3%)		401 (12.4%)	
≥ 8 weeks to < 12 weeks	108 (7.1%)		132 (4.1%)	
≥ 12 weeks to < 16 weeks	66 (4.4%)		112 (3.5%)	
≥ 16 weeks to < 20 weeks	53 (3.5%)		56 (1.7%)	
≥ 20 weeks to < 24 weeks	52 (3.4%)		49 (1.5%)	
≥ 24 weeks to < 28 weeks	105 (6.9%)		167 (5.2%)	
≥ 28 weeks to < 32 weeks	45 (3.0%)		59 (1.8%)	
≥ 32 weeks to < 36 weeks	28 (1.8%)		45 (1.4%)	
≥ 36 weeks to < 40 weeks	22 (1.5%)		40 (1.2%)	
≥ 40 weeks to < 44 weeks	20 (1.3%)		18 (0.6%)	
≥ 44 weeks to < 48 weeks	14 (0.9%)		42 (1.3%)	
≥ 48 weeks to < 52 weeks	11 (0.7%)		28 (0.9%)	
≥ 52 weeks to < 56 weeks	40 (2.6%)		83 (2.6%)	
≥ 56 weeks	749 (49.4%)		1580 (48.8%)	
Total	1515 (100%)	1080.50 (100%)	3239 (100%)	2169.26 (100%)

Table SIII.2.a: By age group				
Indication: Obesity	PLACEBO (n=1515) n (%)		NB (n=3239) n (%)	
Age group	Persons	Person time in years	Persons	Person time in years
18-44 years	686 (45.3%)	445.81 (41.3%)	1443 (44.6%)	920.92 (42.5%)
45-64 years	797 (52.6%)	605.4 (56.0%)	1734 (53.5%)	1207.24 (55.7%)
≥65 years	32 (2.1%)	29.28 (2.7%)	62 (1.9%)	41.10 (1.9%)
Total	1515 (100%)	1080.50 (100%)	3239 (100%)	2169.26 (100%)

Table SIII.2.b: By gender				
Indication: Obesity	PLACEBO (n=1515) n (%)		NB (n=3239) n (%)	
Gender	Persons	Person time in years	Persons	Person time in years
Male	268 (17.7%)	213.45 (19.8%)	549 (16.9%)	420.52 (19.4%)
Female	1247 (82.3%)	867.05 (80.2%)	2690 (83.1%)	1748.74 (80.6%)
Total	1515 (100%)	1080.5 (100%)	3239 (100%)	2169.26 (100%)

Table SIII.3: By ethnicity (by indication)				
Indication: Obesity	PLACEBO (n=1515) n (%)		NB (n=3239) n (%)	
Ethnic origin	Persons	Person time in years	Persons	Person time in years
Hispanic	166 (11.0%)	98.89 (9.2%)	306 (9.4%)	176.27 (8.1%)
Non-Hispanic	1349 (89.0%)	981.60 (90.8%)	2933 (90.6%)	1992.99 (91.9%)
Total	1515 (100%)	1080.5 (100%)	3239 (100%)	2169.26 (100%)

Table SIII.4: By race (by indication)				
Indication: Obesity	PLACEBO (n=1515) n (%)		NB (n=3239) n (%)	
Race	Persons	Person time in years	Persons	Person time in years
White	1193 (78.7%)	861.18 (79.7%)	2477 (76.5%)	1725.91 (79.6%)
Black or African American	261 (17.2%)	177.64 (16.4%)	614 (19.0%)	353.49 (16.3%)
Other	61 (4.0%)	41.68 (3.9%)	148 (4.6%)	89.87 (4.1%)
Total	1515 (100%)	1080.5 (100%)	3239 (100%)	2169.26 (100%)

Table SIII.5: Special populations (by indication)				
Indication: Obesity	PLACEBO (n=1515) n (%)		NB (n=3239) n (%)	
Race	Persons	Person time in years	Persons	Person time in years
Complicated obesity*				
Yes	911 (60.1%)	672.65 (62.3%)	1994 (61.6%)	1368.37 (63.1%)
No	604 (39.9%)	407.85 (37.8%)	1245 (38.4%)	800.9 (36.9%)
Total	1515 (100%)	1080.5 (100%)	3239 (100%)	2169.26 (100%)
Obesity class				
BMI <30 kg/m^2	31 (2.0%)	24.53 (2.3%)	85 (2.6%)	58.51 (2.7%)
30 ≤ BMI <35 kg/m^2	547 (36.1%)	405.97 (37.6%)	1234 (38.1%)	820.85 (37.8%)
35 ≤ BMI <40 kg/m^2	596 (39.3%)	402.88 (37.3%)	1135 (35.0%)	753.83 (34.8%)
BMI ≥40 kg/m^2	341 (22.5%)	247.12 (22.9%)	785 (24.2%)	536.07 (24.7%)
Total	1515 (100%)	1080.5 (100%)	3239 (100%)	2169.26 (100%)

* Complicated obesity is defined as BMI ≥27 and ≤45 kg/m^2 with controlled hypertension and/or dyslipidaemia

To supplement the NB clinical trials programme studies described in Section SIII.2, additional studies (as summarized in the table below) have been performed in specific patient populations as a requirement of marketing approval. Each of the studies below were conducted in the United States. Following the table is a summary of the duration of exposure and the patient demographics for each study. As each of the studies was conducted for a specific purpose in a specific patient population, the data is presented separately for each of these completed clinical trials.

Study	**Description**	**Study design**	**Planned/ actual number of patients**
NB-CVOT	A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Assessing the Occurrence of Major Adverse Cardiovascular Events (MACE) in Overweight and Obese Subjects with Cardiovascular Risk Factors Receiving Naltrexone SR/Bupropion SR	Randomized, double-blind, placebo-controlled	Planned to enroll in the Lead-in: 10,500 subjects Screened: 13,192 subjects Randomized to the Lead-in Period: 10,514 subjects Randomized to the Treatment Period: 8910 subjects - 4454 placebo - 4456 NB32
NaltrexBuprop-4001	A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 4 Study to Assess the Effect of Naltrexone Hydrochloride and Bupropion Hydrochloride Extended Release Combination on the Occurrence of Major Adverse Cardiovascular Events in Overweight and Obese Subjects with Cardiovascular Disease	Randomized, double-blind, placebo-controlled	Screened: 172 Enrolled: 67 Randomized: 58 of 8800 (early termination of study)
NB-404	A Multicenter, Randomized, Open-Label, Controlled, Method-of-Use Study Assessing the Effect of Naltrexone SR/Bupropion SR on Body Weight and Cardiovascular Risk Factors in Overweight and Obese Subjects	Multicenter, randomized, open-label, controlled study designed to assess the CV effects of NB when used in a manner consistent with its intended use after marketing approval	Planned: 198 up to 242 Treated: 242
NaltrexBuprop-1001	A Randomized, Double-Blind, Placebo- and Moxifloxacin Positive Controlled (Open-Label), Cross-Over Study to Evaluate the Potential Effect of Naltrexone and Bupropion Extended-Release Combination on Cardiac Repolarization in Healthy Subjects	Randomized, double-blind, placebo- and moxifloxacin positive-controlled (open-label), 3-way cross-over, cardiac repolarization study	Planned: 84 Randomized: 84 Completed: 69 Analysed: 84
NaltrexBuprop-1004	A Phase 1, Open-Label, Sequential Design Study to Evaluate the Potential Effect of Multiple Oral Doses of Extended-Release Combination of Naltrexone and Bupropion on the Pharmacokinetics of a Single Oral Dose of Metformin in Healthy Subjects	Open-label, sequential-design, drug-drug interaction study	Planned: 30 Enrolled: 30 Completed: 27 Analysed: 30

Study	Description	Study design	Planned/ actual number of patients
NaltrexBu prop-1005	A Phase 1, Open-Label, Parallel Study to Evaluate the Pharmacokinetics of a Single Oral Dose of Extended-Release Combination of Naltrexone and Bupropion in Subjects with Normal Hepatic Function or Varying Degrees of Impaired Hepatic Function	Open-label, parallel-group, single-dose study	Planned: 24-48 Enrolled: 37 Completed: 37 Analysed: 37
NaltrexBu prop-1006	A Phase 1, Open-Label, Parallel Study to Evaluate the Pharmacokinetics of a Single Oral Dose of Extended-Release Combination of Naltrexone and Bupropion in Subjects with Normal Renal Function or Varying Degrees of Impaired Renal Function	Open-label, parallel-group, single-dose study	Planned: 32-48 Enrolled: 37 Completed: 37 Analysed: 37 in Safety dataset; 36 in PK dataset

Study NB-CVOT, Final Dataset: Assessment of the occurrence of MACE in overweight and obese subjects with cardiovascular risk factors

The following is an overview of the exposure to NB in the large, completed cardiovascular outcomes study (NB-CVOT) as well as a description of the population that was exposed to study medication utilizing the final dataset. The original planned study duration included a Screening Period of up to two weeks, a 2-week Lead in Period, and a 3- to 4-year Treatment Period; however, the study was terminated earlier than planned due to administrative study issues as opposed to any safety reasons.

At the time of early termination, the mean duration on study drug during the Treatment Period was 53.08 weeks in the NB32 group and 41.72 weeks in the placebo group. The mean duration for study participation during the Treatment Period was approximately 131 weeks in both groups, and the maximum Treatment Period duration was 160.7 weeks (approximately 3.1 years). The tables to follow summarize the population of patients with long-term exposure. This population was studied in order to assess the occurrence of major adverse cardiac events in overweight and obese individuals with cardiovascular risk factors.

CVOT Table 1: Cumulative duration of exposure (by indication) (Study NB CVOT, Final Data Set)

Indication: Obesity		
Time Interval	Placebo (N=4450)	NB32 (N=4455)
Number of Subjects Receiving Study Medication	4444 (99.9%)	4450 (99.9%)
<2 weeks	108 (2.4%)	218 (4.9%)
≥2 Weeks	4336 (97.4%)	4232 (95.0%)
≥8 Weeks	3979 (89.4%)	3433 (77.1%)
≥16 Weeks	3197 (71.8%)	2845 (63.9%)
≥26 Weeks	1483 (33.3%)	2067 (46.4%)
≥52 Weeks	1167 (26.2%)	1674 (37.6%)
≥78 Weeks	941 (21.1%)	1401 (31.4%)
≥104 Weeks	757 (17.0%)	1170 (26.3%)

CVOT Table 2: Cumulative duration of exposure: Summary Statistics (Study NB CVOT, Final Data Set)		
Indication: Obesity	Placebo (N=4450)	NB32 (N=4455)
Duration on Study Medication (Weeks)[1]		
n	4444	4450
Mean (SD)	41.72 (47.199)	53.08 (55.043)
Median	16.29	18.43
Min, Max	0.1, 157.1	0.1, 158.0
Total Subject-Years on Study Medication	**3553**	**4527**
Duration on Study (Weeks)[2]		
n	4450	4455
Mean (SD)	130.48 (30.372)	131.44 (29.336)
Median	139.00	139.14
Min, Max	0.1, 159.6	0.1, 160.7
Total Subject-Years on Study	**11128**	**11222**
[1] (Last dose date in treatment period - first dose date in treatment period + 1) / 7. [2] (Study discontinuation date in treatment period - randomized date in treatment period + 1) / 7, where the date of study discontinuation is defined as the date of death in deceased subjects and the date of last assessment in other subjects.		

The mean duration on study was similar in both groups, approximately 131 weeks (CSR Table 33). Subjects in the NB32 group stayed on study drug longer than those in the placebo group (mean duration was 53.08 and 41.72 weeks, respectively). Higher percentages of subjects continued placebo up to Week 16 when compared with the NB32 group, although this trend reversed from Week 16 and up to and beyond Week 104, when the percentages of subjects continuing treatment with NB32 were higher than those on placebo.

An overview of patient demographics for the CVOT study is provided in CVOT Table 3.

CVOT Table 3: Summary of Patient Demographics (Study NB CVOT, Final Data Set)			
Indication: Obesity	Treatment Period		
	Placebo (N=4450)	NB32 (N=4455)	Total (N=8905)
Age at Screening (years)			
n	4450	4455	8905
Mean (SD)	60.9 (7.38)	61.1 (7.27)	61.0 (7.33)
Median	61.0	61.0	61.0
Min, Max	45.0, 85.0	45.0, 86.0	45.0, 86.0
<65 years	3053 (68.6%)	2973 (66.7%)	6026 (67.7%)
≥65 years	1397 (31.4%)	1482 (33.3%)	2879 (32.3%)
<70 years	3860 (86.7%)	3867 (86.8%)	7727 (86.8%)
≥70 years	590 (13.3%)	588 (13.2%)	1178 (13.2%)
Sex			
Male	2031 (45.6%)	2018 (45.3%)	4049 (45.5%)
Female	2419 (54.4%)	2437 (54.7%)	4856 (54.5%)
Ethnicity			
Hispanic or Latino	291 (6.5%)	279 (6.3%)	570 (6.4%)
Not Hispanic or Latino	4156 (93.4%)	4174 (93.7%)	8330 (93.5%)
Missing	3 (<0.1%)	2 (<0.1%)	5 (<0.1%)

NaltrexBuprop-4001: A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 4 Study to Assess the Effect of Naltrexone Hydrochloride and Bupropion Hydrochloride Extended Release Combination on the Occurrence of Major Adverse Cardiovascular Events in Overweight and Obese Subjects with Cardiovascular Disease

Due to the early termination of the study, all subjects prematurely discontinued study medication. This study was intended to fulfil a Food and Drug Administration (FDA) and European Medicines Agency (EMA) postmarketing requirement to evaluate long-term treatment of naltrexone hydrochloride and bupropion hydrochloride extended release combination on the incidence of major adverse cardiovascular events (MACE) in obese and overweight subjects with cardiovascular (CV) disease or multiple CV risk factors.

Effective 29 March 2016, Takeda, the original Sponsor of this study, transferred the United States (US) rights of Contrave® to Orexigen Therapeutics, Inc. (now Nalpropion Pharmaceuticals Inc.). Subsequent to the transfer, Orexigen worked with Takeda to understand the operational details underlying the conduct of the study. As stated in correspondence to the study Investigators, Orexigen determined it would not be in a position to transfer study operations and systems from Takeda without a severe interruption in a study conduct and/or a high risk to data integrity. As a result, this study was terminated on 11 April 2016, at which time 58 of the planned 8800 subjects had been randomized in the treatment period, and as such, a synoptic clinical study report (CSR) option was determined appropriate for presenting the collected data for this study.

At the time of early termination, the mean durations on study medication during the Treatment Period in the NB group and in the placebo group were 3.98 and 4.14 weeks, respectively. The mean durations for study participation in the NB group and in the placebo group were 8.21 and 8.78 weeks, respectively, and the maximum durations of study participation in the NB group and in the placebo group were 13.1 and 12.9 weeks, respectively. These data were not combined with the previously presented CVOT data as the extent of exposure is dramatically different due to the early termination of the study.

Table NaltrexBuprop-4001-1: Baseline and Demographic Characteristics, Full Analysis Set

	Placebo (N=30)	NB (N=28)	Total (N=58)
Age (years)[1]			
n	30	28	58
Mean (SD)	65.5 (7.04)	61.3 (9.29)	63.5 (8.40)
Median	65.5	61.5	64.0
Min, Max	46, 79	36, 79	36, 79
<65 years	14 (46.7%)	19 (67.9%)	33 (56.9%)
≥65 years	16 (53.3%)	9 (32.1%)	25 (43.1%)
<70 years	22 (73.3%)	23 (82.1%)	45 (77.6%)
≥70 years	8 (26.7%)	5 (17.9%)	13 (22.4%)
Sex			
Male	21 (70.0%)	22 (78.6%)	43 (74.1%)
Female	9 (30.0%)	6 (21.4%)	15 (25.9%)
Ethnicity			
Hispanic or Latino	2 (6.7%)	2 (7.1%)	4 (6.9%)
Not Hispanic or Latino	28 (93.3%)	26 (92.9%)	54 (93.1%)
Race Grouping			
White	23 (76.7%)	19 (67.9%)	42 (72.4%)
Non-White	7 (23.3%)	9 (32.1%)	16 (27.6%)
American Indian or Alaska Native	0	0	0
Asian	0	1 (3.6%)	1 (1.7%)
Black or African American	7 (23.3%)	7 (25.0%)	14 (24.1%)
Native Hawaiian/Pacific Islander	0	1 (3.6%)	1 (1.7%)
Cardiovascular Disease[2]			

Table NaltrexBuprop-4001-1: Baseline and Demographic Characteristics, Full Analysis Set			
	Placebo (N=30)	**NB (N=28)**	**Total (N=58)**
Coronary Artery Disease	27 (90.0%)	21 (75.0%)	48 (82.8%)
Peripheral Arterial Disease	8 (26.7%)	4 (14.3%)	12 (20.7%)
Cerebrovascular Disease	7 (23.3%)	12 (42.9%)	19 (32.8%)
Smoking Classification			
Never Smoked	10 (33.3%)	13 (46.4%)	23 (39.7%)
Current Smoker	3 (10.0%)	3 (10.7%)	6 (10.3%)
Ex-smoker	17 (56.7%)	12 (42.9%)	29 (50.0%)
Weight (kg)			
n	30	28	58
Mean (SD)	107.38 (20.138)	115.05 (21.970)	111.08 (21.211)
Median	102.65	115.95	110.85
Min, Max	71.0, 145.1	68.4, 150.0	68.4, 150.0
Height (cm)			
n	30	28	58
Mean (SD)	171.72 (8.525)	174.36 (10.318)	172.99 (9.443)
Median	172.40	175.10	174.75
Min, Max	156.9, 188.0	152.0, 190.5	152.0, 190.5
BMI (kg/m^2)			
n	30	28	58
Mean (SD)	36.38 (5.308)	37.75 (7.192)	37.04 (6.270)
Median	35.10	36.85	35.80
Min, Max	27.8, 48.0	27.4, 57.3	27.4, 57.3
<35 kg/m^2	15 (50.0%)	11 (39.3%)	26 (44.8%)
≥35 to <40 kg/m^2	8 (26.7%)	7 (25.0%)	15 (25.9%)
≥40 kg/m^2	7 (23.3%)	10 (35.7%)	17 (29.3%)
<30 kg/m^2	2 (6.7%)	3 (10.7%)	5 (8.6%)
≥30 to <35 kg/m^2	13 (43.3%)	8 (28.6%)	21 (36.2%)
≥35 to <40 kg/m^2	8 (26.7%)	7 (25.0%)	15 (25.9%)
≥40 kg/m^2	7 (23.3%)	10 (35.7%)	17 (29.3%)

NB = Naltrexone/Bupropion.
Note: For randomized subjects, baseline is defined as the last observation collected on or before Study Day 1 of the treatment period.
Note: Denominator for percentages is the number of subjects in the Full Analysis Set, except for the subgroups of age and BMI, which use the number of observations as denominator.
[1] Integer part of [(date of informed consent — date of birth + 1)/365.25].
[2] Subjects may have more than one type of CV disease.

NB-404: Evaluation of the CV effects of NB when used in a manner consistent with its intended use after marketing approval

The following is an overview of the exposure to NB and the population demographics for this study designed to assess the effects of NB, used in a manner consistent with its intended use after marketing approval, on body weight and cardiovascular risk factors compared to the effects of Usual Care in subjects who were overweight with dyslipidemia and/or controlled hypertension or obese. The study design included a Screening Period (up to 2 weeks), a Controlled Treatment Period (Day 1 to Week 26), and an Uncontrolled Treatment Period (Week 26 to Week 78). As the prior placebo-controlled ISS dataset did not include patients that also underwent comprehensive lifestyle intervention, these data are presented separately.

Table NB-404-1: Exposure and Medication Compliance at Week 78 - ITT Population		
Variable	**Usual Care/NB + CLI (N=89)**	**NB + CLI (N=153)**
Total time on study drug (weeks)		
N	89	153
Mean (SD)	29.2 (19.4)	39.1 (32.7)
Median	19.7	17.7
Min, max	0.4, 56.3	0.3, 82.0
Total time in study (weeks)		
N	89	153
Mean (SD)	62.6 (21.5)	58.9 (28.2)
Median	77.6	77.0
Min, max	2.1, 81.3	1.9, 82.0
Medication compliance through Week 78 (%)[a]		
N	79	152
Mean (SD)	95.9 (14.1)	94.6 (13.5)
Median	100.0	100.0
Min, max	7.0, 100.0	18.8, 100.0
Compliance <80%, n (%)	5 (5.6)	16 (10.5)
Compliance ≥80%, n (%)	74 (83.1)	136 (88.9)

CLI = comprehensive lifestyle intervention, max = maximum, min = minimum, NB = naltrexone/bupropion combination sustained-release tablet, SD = standard deviation.
a: The ratio of the total number of days subjects took study medication which is the number of days between Day 1 and last NB dose (inclusive) on which NB compliance CRF was last completed minus the number of days the subject missed both the morning and evening dose up to the last NB dose, and the number of days in the same interval above.

Table NB-404-1: Summary of Patient Demographics (ITT Population)			
Variable Category or Statistic	**Usual Care/NB+CLI (N=89)**	**NB+CLI (N=153)**	**Total (N=242)**
Age (years) at Screening			
n	89	153	242
Mean (SD)	47.0 (9.98)	46.1 (9.66)	46.5 (9.77)
Median	49.0	48.0	49.0
Min, Max	21, 60	20, 60	20, 60
Sex [(n %)]			
Female	77 (86.5)	125 (81.7)	202 (83.5)
Male	12 (13.5)	28 (18.3)	40 (16.5)
Race [(n %)]			
White	64 (71.9)	124 (81.0)	188 (77.7)
Black or African American	24 (27.0)	28 (18.3)	52 (21.5)
Asian	0 (0.0)	1 (0.7)	1 (0.4)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
American Indian or Alaskan Native	1 (1.1)	0 (0.0)	1 (0.4)
Other	0 (0.0)	0 (0.0)	0 (0.0)

Table NB-404-1: Summary of Patient Demographics (ITT Population)			
Variable Category or Statistic	**Usual Care/NB+CLI (N=89)**	**NB+CLI (N=153)**	**Total (N=242)**
Ethnicity [(n %)]			
Hispanic or Latino	5 (5.6)	4 (2.6)	9 (3.7)
Not Hispanic or Latino	84 (94.4)	149 (97.4)	233 (96.3)
Height (cm) at Screening			
n	89	153	242
Mean (SD)	165.94 (7.875)	166.86 (7.906)	166.52 (7.891)
Median	165.10	166.30	166.00
Min, Max	152.5, 191.5	151.0, 190.5	151.0, 191.5
Weight (kg) at Baseline			
n	89	153	242
Mean (SD)	100.23 (16.577)	101.36 (15.091)	100.94 (15.629)
Median	96.70	98.20	98.00
Min, Max	69.1, 140.9	70.7, 143.8	69.1, 143.8
BMI (kg/m^2) at Baseline			
n	89	153	242
Mean (SD)	36.26 (4.369)	36.33 (4.200)	36.31 (4.254)
Median	35.30	35.61	35.59
Min, Max	28.7, 44.9	27.8, 44.8	27.8, 44.9
Baseline BMI category [(n %)]			
<35 kg/m^2	41 (46.1)	70 (45.8)	111 (45.9)
³35 to <40 kg/m^2	28 (31.5)	49 (32.0)	77 (31.8)
³40 kg/m^2	20 (22.5)	34 (22.2)	54 (22.3)
<30 kg/m^2	5 (5.6)	3 (2.0)	8 (3.3)

NaltrexBuprop-1001: Evaluation of NB's potential effect on cardiac repolarization in healthy subjects

The following is an overview of the population demographics exposed to study medication in this thorough QT study. The exposure to study drug for patients in this study involved a randomized sequence (ABC, BCA, CAB, ACB, BAC, CBA) where Treatment A was NB for 11 days, Treatment B was Placebo for 11 days, and Treatment C was Placebo for 10 days followed by moxifloxacin for 1 day. The extent of exposure and the characteristics of these patients are presented separate from the ISS data set as it is not expected that this population of non-overweight or obese, healthy subjects participating in this 3-way crossover cardiac repolarization study will be indicative of that which will use this product in clinical practice.

Table NaltrexBuprop-1001-1A: Summary of Patient Demographics				
	Sequence ABC (N=14)	Sequence BCA (N=14)	Sequence CAB (N=14)	Sequence ACB (N=14)
Age (Years)				
n	14	14	14	14
Mean (SD)	37.6 (8.45)	38.8 (7.61)	36.1 (9.29)	37.2 (9.91)
Median	37.5	39.0	37.5	37.0
Minimum, Maximum	25, 54	27, 53	20, 52	23, 53

Table NaltrexBuprop-1001-1A: Summary of Patient Demographics				
	Sequence ABC (N=14)	Sequence BCA (N=14)	Sequence CAB (N=14)	Sequence ACB (N=14)
Sex, n(%)				
Male	8 (57.1)	8 (57.1)	7 (50.0)	7 (50.0)
Female	6 (42.9)	6 (42.9)	7 (50.0)	7 (50.0)
Ethnicity, n(%)				
Hispanic or Latino	6 (42.9)	4 (28.6)	6 (42.9)	5 (35.7)
Not Hispanic or Latino	8 (57.1)	10 (71.4)	8 (57.1)	9 (64.3)
Race, n(%)				
American Indian or Alaskan Native	0	0	0	0
Asian	1 (7.1)	0	0	0
Black or African American	5 (35.7)	6 (42.9)	6 (42.9)	6 (42.9)
Native Hawaiian or Other Islander	0	0	0	0
White	8 (57.1)	8 (57.1)	8 (57.1)	8 (57.1)
Multiracial	0	0	0	0
Height (cm)				
n	14	14	14	14
Mean (SD)	171.7 (9.08)	173.1 (10.31)	170.6 (9.97)	166.4 (9.09)
Median	174.5	177.5	170.5	164.0
Minimum, Maximum	150, 185	152, 185	154, 188	151, 185
Weight (kg)				
n	14	14	14	14
Mean (SD)	81.05 (18.582)	89.04 (10.948)	82.37 (14.462)	73.42 (10.796)
Median	78.30	90.70	83.40	73.45
Minimum, Maximum	51.9, 117.3	69.2, 111.8	59.7, 104.8	57.2, 90.6
Body Mass Index (kg/m^2)				
n	14	14	14	14
Mean (SD)	27.23 (4.452)	29.69 (2.462)	28.14 (3.271)	26.61 (3.938)
Median	27.21	30.12	28.19	27.26
Minimum, Maximum	20.0, 34.3	25.4, 32.7	21.1, 34.2	21.3, 32.6
Smoking Classification, n(%)				
Subject has never smoked	13 (92.9)	11 (78.6)	13 (92.9)	12 (85.7)
Subject is a current smoker	0	0	0	0
Subject is an ex-smoker	1 (7.1)	3 (21.4)	1 (7.1)	2 (14.3)
Female Reproductive Status, n(%)				
Postmenopausal	0	0	0	0
Surgically Sterile	2 (14.3)	5 (35.7)	4 (28.6)	1 (7.1)
Female of Childbearing Potential	4 (28.6)	1 (7.1)	3 (21.4)	6 (42.9)
N/A (Subject is Male)	8 (57.1)	8 (57.1)	7 (50.0)	7 (50.0)

Table NaltrexBuprop-1001-1B: Summary of Patient Demographics			
	Sequence BAC (N=14)	Sequence CBA (N=14)	Total (N=84)
Age (Years)			
n	14	14	84
Mean (SD)	36.9 (10.45)	36.2 (8.47)	37.1 (8.85)
Median	36.0	35.0	36.0
Minimum, Maximum	21, 51	23, 55	20, 55
Sex, n(%)			
Male	8 (57.1)	7 (50.0)	45 (53.6)
Female	6 (42.9)	7 (50.0)	39 (46.4)
Ethnicity, n(%)			
Hispanic or Latino	5 (35.7)	5 (35.7)	31 (36.9)
Not Hispanic or Latino	9 (64.3)	9 (64.3)	53 (63.1)
Race, n(%)			
American Indian or Alaskan Native	0	0	0
Asian	1 (7.1)	0	2 (2.4)
Black or African American	6 (42.9)	6 (42.9)	35 (41.7)
Native Hawaiian or Other Islander	0	0	0
White	7 (50.0)	8 (57.1)	47 (56.0)
Multiracial	0	0	0
Height (cm)			
n	14	14	84
Mean (SD)	169.1 (7.35)	169.1 (8.85)	170.0 (9.14)
Median	169.5	167.0	170.0
Minimum, Maximum	156, 182	159, 186	150, 188
Weight (kg)			
n	14	14	84
Mean (SD)	77.91 (13.253)	79.80 (14.199)	80.60 (14.337)
Median	80.25	80.15	81.10
Minimum, Maximum	58.6, 97.0	50.5, 104.9	50.5, 117.3
Body Mass Index (kg/m^2)			
n	14	14	84
Mean (SD)	27.24 (4.258)	27.77 (3.484)	27.78 (3.724)
Median	27.56	27.86	28.19
Minimum, Maximum	20.6, 34.2	19.7, 31.8	19.7, 34.3
Smoking Classification, n(%)			
Subject has never smoked	14 (100.0)	12 (85.7)	75 (89.3)
Subject is a current smoker	0	0	0
Subject is an ex-smoker	0	2 (14.3)	9 (10.7)
Female Reproductive Status, n(%)			
Postmenopausal	0	0	0
Surgically Sterile	2 (14.3)	0	14 (16.7)
Female of Childbearing Potential	4 (28.6)	7 (50.0)	25 (29.8)
N/A (Subject is Male)	8 (57.1)	7 (50.0)	45 (53.6)

NaltrexBuprop-1004: Evaluation of NB's potential effect (multiple doses) on the pharmacokinetics of a single oral dose of metformin in healthy subjects

Following is an overview of the population demographics exposed to study medication in this drug-drug interaction study. All subjects received NB for 13 days (NB 8 mg/90 mg BID for 3 days, then NB 16 mg/180 mg BID for 10 days) followed by a single dose of Metformin HCl 850 mg. The extent of exposure and the characteristics of these patients are presented separate from the ISS data set as it is not expected that this population of non-overweight or obese, healthy subjects participating in this pharmacokinetic study will be indicative of that which will use this product in clinical practice.

Table NaltrexBuprop-1004-1: Summary of Patient Demographics	
	Total (N=30)
Age (Years)	
N	30
Mean (SD)	31.4 (6.86)
Median	31.5
Minimum, Maximum	19, 46
Sex (n[%])	
Male	22 (73.3)
Female	8 (26.7)
Ethnicity (n[%])	
Hispanic or Latino	13 (43.3)
Not Hispanic or Latino	17 (56.7)
Race (n[%])	
American Indian or Alaskan Native	0
Asian	0
Black or African American	11 (36.7)
Native Hawaiian or Other Pacific Islander	0
White	18 (60.0)
Multiracial	1 (3.3)
Height (cm)	
n	30
Mean (SD)	172.0 (9.87)
Median	171.5
Minimum, Maximum	149, 194
Weight (kg)	
n	30
Mean (SD)	91.72 (18.518)
Median	91.00
Minimum, Maximum	61.1, 136.9
Body Mass Index (kg/m^2)	
n	30
Mean (SD)	31.05 (5.634)
Median	31.83
Minimum, Maximum	20.3, 38.9
Smoking Classification (n[%])	
Subject has never smoked	26 (86.7)
Subject is a current smoker	0
Subject is an ex-smoker	4 (13.3)
Female Reproductive Status	
Postmenopausal	0
Surgically Sterile	1 (3.3)
Female of Childbearing Potential	7 (23.3)
N/A (Subject is Male)	22 (73.3)

NaltrexBuprop-1005: Study of Pharmacokinetics of NB in Subjects with Hepatic impairment - Demographics and Baseline Characteristics

The following is an overview of the population demographics exposed to study medication in this hepatic impairment pharmacokinetic study. The extent of exposure and the characteristics of these patients are presented separate from the ISS data set as this is a single dose pharmacokinetic study.

Statistics	Normal Hepatic Function Group (N=13)	Mild Hepatic Impairment Group (N=8)	Moderate Hepatic Impairment Group (N=8)	Severe Hepatic Impairment Group (N=8)	Overall (N=37)
Age (years)					
Mean (SD)	57.9 (7.11)	58.5 (3.78)	60.1 (5.38)	54.9 (7.26)	57.9 (6.22)
Median	55.0	60.0	62.5	55.5	57.0
Min, Max	51, 71	52, 62	52, 67	46, 66	46, 71
Sex, n (%)					
Male	10 (76.9%)	7 (87.5%)	7 (87.5%)	5 (62.5%)	29 (78.4%)
Female	3 (23.1%)	1 (12.5%)	1 (12.5%)	3 (37.5%)	8 (21.6%)
Race, n (%)					
American Indian or Alaska Native	1 (7.7%)	0	0	0	1 (2.7%)
Asian	0	1 (12.5%)	0	0	1 (2.7%)
Black or African American	0	1 (12.5%)	1 (12.5%)	0	2 (5.4%)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
White	12 (92.3%)	6 (75.0%)	7 (87.5%)	8 (100.0%)	33 (89.2%)
Ethnicity, n (%)					
Hispanic or Latino	10 (76.9%)	4 (50.0%)	5 (62.5%)	6 (75.0%)	25 (67.6%)
Not Hispanic or Latino	3 (23.1%)	4 (50.0%)	3 (37.5%)	2 (25.0%)	12 (32.4%)
Screening Height (cm)					
Mean (SD)	172.32 (6.966)	169.81 (9.910)	171.78 (4.001)	167.15 (11.109)	170.54 (8.157)
Median	172.50	172.75	171.00	166.25	171.50
Min, Max	156.0, 180.6	156.0, 182.5	166.5, 178.2	152.0, 186.1	152.0, 186.1
Screening Weight (kg)					
Mean (SD)	81.33 (12.035)	74.56 (9.276)	87.14 (12.261)	78.16 (11.139)	80.44 (11.724)
Median	80.40	71.90	89.35	77.80	78.40
Min, Max	63.9, 103.7	65.2, 93.2	66.7, 101.4	60.3, 95.9	60.3, 103.7
Screening BMI (kg/m^2)					
Mean (SD)	27.34 (3.238)	26.13 (4.836)	29.54 (3.995)	28.36 (5.851)	27.77 (4.387)
Median	27.80	25.65	29.80	28.45	27.10
Min, Max	21.5, 34.4	20.7, 36.4	23.5, 34.5	20.1, 38.0	20.1, 38.0
Smoking Status, n (%)					
Smoker	4 (30.8%)	4 (50.0%)	1 (12.5%)	2 (25.0%)	11 (29.7%)
Non-smoker	9 (69.2%)	4 (50.0%)	7 (87.5%)	6 (75.0%)	26 (70.3%)
Female Reproductive Status, n (%)					
Sterile	0	0	1 (12.5%)	0	1 (2.7%)
Post-menopausal	3 (23.1%)	1 (12.5%)	0	2 (25.0%)	6 (16.2%)
Potentially able to bear children	0	0	0	1 (12.5%)	1 (2.7%)
N/A (Subject is male)	10 (76.9%)	7 (87.5%)	7 (87.5%)	5 (62.5%)	29 (78.4%)
Child-Pugh Score					
Mean (SD)	NA	5.8 (0.46)	7.8 (0.89)	10.9 (0.99)	8.1 (2.29)
Median	NA	6.0	7.5	10.5	7.5
Min, Max	NA	5, 6	7, 9	10, 12	5, 12

Statistics	Normal Hepatic Function Group (N=13)	Mild Hepatic Impairment Group (N=8)	Moderate Hepatic Impairment Group (N=8)	Severe Hepatic Impairment Group (N=8)	Overall (N=37)
Abbreviations: BMI, body mass index; NA, not applicable.					
Note 1: Percentages are based on the number of subjects in the Safety Set in each group and overall.					
Note 2: Hepatic impairment groups are based on the Child-Pugh Score classification of Mild Hepatic Impairment (5-6), Moderate Hepatic Impairment (7-9), or Severe Hepatic Impairment (10-15).					
Note 3: Normal Hepatic Function, Mild Hepatic Impairment, Moderate Hepatic Impairment groups received naltrexone 16 mg/bupropion 180 mg and Severe Hepatic Impairment group received naltrexone 8 mg/bupropion 90 mg.					
(a) All 13 (100.0%) subjects with normal hepatic function had prothrombin time prolonged (sec) of less than 4 seconds (Source: Data Listing 16.2.8.1). Source: Table 14.1.5.					

NaltrexBuprop-1006: Study of Pharmacokinetics of NB in Subjects with Renal Impairment- Demographics and Baseline Characteristics

The following is an overview of the population demographics exposed to study medication in this renal impairment pharmacokinetic study. The extent of exposure and the characteristics of these patients are presented separate from the ISS data set as this is a single dose pharmacokinetic study.

	Normal Renal Function Group (N=13)	Mild Renal Impairment Group (N=9)	Moderate Renal Impairment Group (N=8)	Severe Renal Impairment Group (N=7)	Overall (N=37)
Age (years)					
Mean (SD)	62.9 (4.70)	66.6 (6.69)	67.4 (5.83)	61.3 (8.38)	64.5 (6.44)
Median	65.0	67.0	68.5	63.0	66.0
Min, Max	57, 69	54, 75	59, 74	47, 69	47, 75
Sex, n (%)					
Male	7 (53.8%)	3 (33.3%)	6 (75.0%)	5 (71.4%)	21 (56.8%)
Female	6 (46.2%)	6 (66.7%)	2 (25.0%)	2 (28.6%)	16 (43.2%)
Race, n (%)					
American Indian or Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Black or African American	2 (15.4%)	0	2 (25.0%)	0	4 (10.8%)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
White	11 (84.6%)	9 (100.0%)	6 (75.0%)	7 (100.0%)	33 (89.2%)
Ethnicity, n (%)					
Hispanic or Latino	4 (30.8%)	1 (11.1%)	3 (37.5%)	5 (71.4%)	13 (35.1%)
Not Hispanic or Latino	9 (69.2%)	8 (88.9%)	5 (62.5%)	2 (28.6%)	24 (64.9%)
Screening Height (cm)					

	Normal Renal Function Group (N=13)	Mild Renal Impairment Group (N=9)	Moderate Renal Impairment Group (N=8)	Severe Renal Impairment Group (N=7)	Overall (N=37)
Mean (SD)	166.37 (8.683)	162.51 (9.922)	171.04 (10.179)	166.00 (6.322)	166.37 (9.078)
Median	165.20	166.00	172.80	163.10	166.00
Min, Max	153.9, 180.6	149.0, 177.5	151.1, 182.2	161.1, 179.1	149.0, 182.2
Screening Weight (kg)					
Mean (SD)	79.31 (13.670)	80.24 (17.620)	86.39 (9.555)	84.77 (16.704)	82.10 (14.307)
Median	75.50	76.60	87.00	88.90	81.90
Min, Max	57.5, 99.6	55.9, 109.7	71.4, 102.4	58.4, 107.2	55.9, 109.7
Screening BMI (kg/m^2)					
Mean (SD)	28.55 (3.621)	30.16 (4.576)	29.70 (3.885)	30.73 (5.798)	29.60 (4.276)
Median	28.80	30.40	29.50	31.20	29.30
Min, Max	22.3, 35.8	23.6, 36.8	23.9, 35.2	22.2, 40.3	22.2, 40.3
Smoking Status, n (%)					
Smoker	1 (7.7%)	1 (11.1%)	1 (12.5%)	0	3 (8.1%)
Non-smoker	12 (92.3%)	8 (88.9%)	7 (87.5%)	7 (100.0%)	34 (91.9%)
Female Reproductive Status, n (%)					
Sterile	1 (7.7%)	0	0	0	1 (2.7%)
Post-menopausal	5 (38.5%)	6 (66.7%)	2 (25.0%)	2 (28.6%)	15 (40.5%)
Potentially able to bear children	0	0	0	0	0
N/A (Subject is male)	7 (53.8%)	3 (33.3%)	6 (75.0%)	5 (71.4%)	21 (56.8%)
Screening CrCl-BSA (mL/min)					
Mean (SD)	114.0 (23.87)	73.9 (9.96)	44.9 (6.08)	20.4 (4.04)	71.6 (39.25)
Median	107.0	75.0	44.0	22.0	69.0
Min, Max	93, 175	61, 86	36, 53	15, 25	15, 175

Abbreviations: BMI, body mass index; CrCl-BSA, creatinine clearance based on 24-hour urinary creatinine excretion with body surface area adjustment; N/A, not applicable.

Note: Percentages are based on the number of subjects in the Safety Set in each group and overall.

Part II: Module SIV - Populations not studied in clinical trials

The active components of NB (naltrexone HCl and bupropion HCl) have been approved and marketed in Europe since 1984 and 1999, respectively, during which time over 500,000 patients have received naltrexone HCl and 10 million patients have received bupropion HCl. In the US, over 1 million and 50 million patients have received naltrexone HCl and bupropion HCl, respectively. Over the course of the NB clinical development programme, a total of 24 prospective human trials (15 Phase 1, 5 Phase 2, and four Phase 3 trials) have been completed. In the integrated safety analysis database, 3239 subjects (2169 person-years) were cumulatively exposed to NB across 3 dosing groups (NB16, NB32, NB48/50). In total, 4754 subjects (NB exposed = 3239 and placebo = 1515) were included in the primary analysis dataset from NB clinical trials and were followed a median of 55 weeks (3250 person-years). The 1515 placebo subjects form the basis of the unexposed comparator population, contributing to 1081 person-years of follow-up.

The clinical trials evidence that supports NB includes a broadly representative selection of obese subjects and include subjects with both uncomplicated and complicated obesity. Consistent with the Committee for Medicinal Products for Human Use (CHMP) guidance on weight management products, Studies NB-301, NB-302 and NB-303 enrolled subjects with a BMI ≥30 and ≤45 kg/m^2 for subjects with uncomplicated obesity or with a BMI ≥27 and ≤45 kg/m^2 for obese or overweight subjects with controlled hypertension and/or dyslipidaemia. Also, as recommended by the CHMP guidance, one study (Study NB-304) was conducted in obese and overweight subjects with type 2 diabetes.

Subjects entering the NB clinical trial programme were required to have a level of obesity that is associated with a significant health risk and an increased risk of mortality. Thus, the populations studied in the NB clinical trials programme are generally representative of the target population in terms of the severity of disease and the presence of comorbid conditions. Nonetheless, randomised controlled trials have known limitations with regard to capturing rare adverse reactions, detecting the effects of prolonged exposures, understanding cumulative effects, and finding latent adverse events. The implications for the NB target population resulting from the limitations of the trial programme are discussed below.

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

The following summarize the important exclusion criteria across the development program:

Criterion: Uncontrolled hypertension and Cardiovascular disease

Reason for exclusion: In the NB clinical trials programme, subjects receiving treatment for hypertension or hyperlipidaemia, who were not on a stable regimen, were excluded. Subjects with a severe cardiac abnormality, as well as those with MI, stroke, class III or IV CHF were also excluded from study. These exclusions were aimed at removing unstable subjects who might be less able to complete the clinical trials.

Is it to be considered a missing information: No

Rationale: The NB-CVOT placebo-controlled study included 4,450 patients with exposure to the fixed combination and 4,455 on placebo. These patients were included in this study by virtue of having documented cardiac risk factors. The final results from the analysis of the NB-CVOT study designed to evaluate the impact of NB therapy on major adverse cardiovascular events in obese subjects with increased cardiovascular risks do not suggest an increased risk for major cardiovascular events. In the NB double-blind clinical trials, discontinuations due to a hypertension related event were rare both in NB treated subjects (n=23/3239,0.7%) as well as in those treated with placebo (n=3/1515, 0.02%). Discontinuations due to an arrhythmia related event were rare both in NB treated subjects (n=20/3,239, 0.6%) as well as in those treated with placebo (n=8/1,515, 0.05%). Palpitations infrequently led to discontinuations (0.3% for NB; none for placebo). Discontinuations due a tachyarrhythmia related event were rare and less frequent in the NB group compared with placebo (<0.1% vs. 0.2%). Overall Subjects with a history of cardiovascular disease and/or cardiovascular risk factors were included in the Phase 3 programme and there is no evidence to suggest that the NB safety and efficacy profile would be adversely altered as a result of underlying cardiovascular disease or major cardiovascular risk factors.

Criterion: Hepatic insufficiency

Reason for exclusion: The potential effects of hepatic impairment come from data from available literature and approved product information on bupropion HCl and naltrexone HCl. Most drugs are cleared by liver and/or kidneys, any factor that affects their function can result in altered blood levels and may lead to altered benefit-risk of the product. Patients with liver disease are also a subgroup at higher risk for morbidity and mortality, excluding such patients reduces the risk of adverse events caused by underlying conditions and concomitant drugs and reduces the difficulty in deciding whether an adverse event should be attributed to the pre-existing condition or to the test drug.

Is it to be considered a missing information: Yes

Criterion: Renal insufficiency

Reason for exclusion: NB has not been studied in subjects with renal insufficiency. The identified potential effects of renal impairment come from data from available literature and approved product information on bupropion HCl and naltrexone HCl. Most drugs are cleared by liver and/or kidneys, any factor that affects their function can result in altered blood levels and may lead to altered benefit-risk of the product. Patients with renal disease are also a subgroup at higher risk for morbidity and mortality, excluding such patients reduces the risk of adverse events caused by underlying conditions and concomitant drugs and reduces the difficulty in deciding whether an adverse event should be attributed to the pre-existing condition or to the test drug.

Is it to be considered a missing information: Yes

Criterion: Seizures

Reason for exclusion: Based upon the historical experience with bupropion and its association with seizures, the use of NB in patients with history of seizures would not be advisable, and therefore seizure disorder or history of seizures, along with bulimia and anorexia nervosa and known central nervous system tumour are included on the list of contraindications.

Is it to be considered a missing information: No

Rationale: Given the over 3 decades of experience with bupropion in clinical practice, considerable information on the association of bupropion and the occurrence of seizures is available. The incidence of seizure in subjects receiving NB in clinical trials was approximately 0.06% (2/3239 subjects) vs. 0.0% (0/1515 subjects) on placebo. This incidence of seizure, along with incidence of seizure in subjects who received NB in a large cardiovascular outcome trial (CVOT), was no higher than the seizure rate with bupropion as a single agent at approved doses.

Criterion: Psychiatric conditions (excluding bipolar disorder, bulimia and anorexia nervosa)

Reason for exclusion: Subjects with serious psychiatric conditions and those required medications for the treatment of a psychiatric disorder (with the exception of short-term insomnia) within the previous 6 months were excluded from the phase 3 studies. These exclusions were aimed at removing unstable subjects who might be less able to complete the clinical trials.

Is it to be considered a missing information: No

Rationale: Study NB-CVOT allowed enrolment of subjects with depression and anxiety. This placebo-controlled study included 4,450 patients with exposure to the fixed combination and 4,455 on placebo. Bupropion HCl, a major constituent of the NB combination, is well characterised across a variety of psychiatric conditions and is authorised as an efficacious treatment for major depression.

Criterion: Pregnancy, fertility, and lactation

Reason for exclusion: Pregnant females and females who were not willing to utilize appropriate contraception methods were excluded from the study because of the clear impact of pregnancy on bodyweight, given that a primary objective of the Phase 3 programme was to isolate the drug effect of NB on weight. Further uncertainty regarding the risk of adverse events in pregnant or lactating women and their foetuses or new-borns has historically led to their exclusion from research.

Is it to be considered a missing information: Yes

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect rare adverse reactions attributable to the fixed combination as opposed to the mono components, adverse reactions with a long latency, or those that may be caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Type of special population	**Exposure**
Children (less than 18 years of age)	NB has not been studied in paediatric patients. The safety and efficacy of NB in children and adolescents below 18 years have not been established.
Elderly patients (65 years and older)	Few subjects over the age of 65 received NB in the completed Phase 3 trials of the NB clinical development programme (n=62). In contrast, the NB cardiovascular outcomes study (NB-CVOT Study) includes a substantial proportion of subjects who were ≥65 years of age (32.3%, n=2,879 [n=1,397 placebo and n=1,482 NB]). Further, 1,178 subjects (13.2%) were ≥75 years of age (n=590 placebo and n=588 NB). Completed clinical studies supporting the registration of NB did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.
Pregnant/Breastfeeding women	In the NB clinical development programme, 28 women exposed to NB or placebo became pregnant (21 NB subjects, 7 placebo subjects). Of the 21 subjects who became pregnant after receiving naltrexone HCl and bupropion HCl in combination, one subject received a single dose of naltrexone HCl SR 16 mg/ bupropion HCl SR 180 mg (as part of Study NB-229), two received NB16 (for up to 161 days), 16 received NB32 (for up to 396 days), and two subjects in Study NB-303 received NB48 (for up to approximately 167 days) following re-randomisation after receiving NB32 for up to approximately 241 days. Of those who became pregnant after taking NB, all but one had at least 7 days of foetal exposure based on having a positive serum pregnancy test within 2 weeks of the last dose of study drug. One subject received only a single dose of active study medication, at the dose of naltrexone HCl prolonged-release 16 mg/bupropion HCl prolonged-release 180 mg. Moreover, 11 subjects carried to term and gave birth to healthy infants, 3 subjects had elective terminations with no record of congenital defect, 4 subjects experienced spontaneous miscarriages (1 was reported to have a history of miscarriages, 1 had a history of ectopic pregnancy, and 1 was reported to have an intrauterine device in place at the time of the miscarriage), and the outcomes of 3 pregnancies were unknown (subjects were lost to follow-up). There were no reports of congenital anomaly.

Type of special population	**Exposure**
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment	<u>Hepatic impairment</u> 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. Additionally, bupropion is metabolised to its major active metabolite hydroxybupropion primarily by hepatic cytochrome P450 CYP2B6; thus, the potential exists for interaction when administered with medications 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 medications metabolised by CYP2D6. Patients with hepatic impairment may have altered function of these cytochrome systems. In the post-approval setting, NB was evaluated in 37 patients in a Phase 1, open label, parallel group, single dose study (NaltrexBuprop1005). The study included patients with normal hepatic function as well as with hepatic impairment classified as mild, moderate, or severe hepatic impairment as defined by the Child-Pugh classification system, A (mild), B (moderate), or C (severe). It was concluded that 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). 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. It was also concluded that patients with severe or moderate hepatic impairment may have higher drug concentrations which may result in an increase in adverse drug reactions. <u>Renal impairment</u> A substantial proportion of subjects in Study NB-CVOT (26.9%; n=2,394, placebo n=1,174; NB n=1220) exhibited mild or moderate renal impairment (eGFR 30 to 90 mL/min) at screening; 3.9% of these subjects were classified as having moderate renal impairment (n=348; eGFR 30-59 mL/min). Based on the data in these 2,394 patients, the safety profile of patients with mild renal failure has been characterized and is shown to be similar to that for patients without renal impairment. The identified potential effects of renal impairment come from data from available literature and approved product information on bupropion HCl and naltrexone HCl. A single-dose pharmacokinetic study has been conducted for naltrexone / bupropion in 37 patients in a Phase 1, open label, parallel group study (NaltrexBuprop1006). The study evaluated patients with varying degrees of renal function (normal renal function or mild, moderate, or severe renal impairment). 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.

Type of special population	**Exposure**
Population with relevant different ethnic origin	Analysis of adverse events and vital signs within the integrated NB datasets indicated no clinically meaningful differences by race or ethnicity. Bupropion HCl is metabolised by hepatic CYP2B6. The effects of gender, ethnicity, and genetic polymorphism on hepatic CYP2B6 (cytochrome P450 2B6) expression and activity have been previously demonstrated in vitro. Race/ethnic differences in CYP2B6 genotype and phenotype were observed only in women. CYP2B6 genotype is the most important patient variable for predicting the level of CYP2B6 activity in women when measured by the metabolism of bupropion HCl. The bupropion HCl metabolic ratio appears to detect known differences in CYP2B6 activity associated with genetic polymorphism, across different ethnic groups. Small differences in mean naltrexone HCl C_{max} values were observed between Black and White subgroups (approximately 25% higher in Whites) in the non-compartmental analysis PK summary, which compiled data under fasting conditions only. In contrast, in the population PK analysis, clearance of naltrexone HCl was 34% lower in the non-White subgroups relative to the White subgroup, which would predict higher AUC values in non-whites compared with Whites. Unequal distribution of body size, gender, and relative proportions of fed study data were possible confounding factors in this analysis. No genetic variation in PK is predicted (based on the metabolism of naltrexone HCl) and none has been reported. Overall, the perceived differences between subsets in the various analyses was small, unlikely to be clinically meaningful, and may have been attributable more to the considerable inter-subject variability of naltrexone HCl rather than any true genetic differences. Based on data from the NB clinical development programme, there are no separate dosing recommendations for patients with differing ethnicity.
Sub-populations carrying known and relevant polymorphisms	No pharmacogenetic variation has been predicted or reported in NB or during the clinical development programme for NB.
Patients with other relevant co-morbidity	Results of the NB clinical trials programme showed that the frequency and severity of AEs reported by obese/overweight subjects with type 2 diabetes was generally similar to those reported by subjects without diabetes, with the exception of increased nausea, vomiting, diarrhoea, and hypertension AEs relative to placebo. Relative to placebo, changes in blood pressure in subjects with diabetes were generally similar to or less than that observed in subjects without diabetes. No clinically meaningful differences were observed in other subpopulations (e.g. age, ethnicity, race, gender, baseline smoking status, baseline antihypertensive medication, by ≥5% weight loss at endpoint, and obesity class).

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Non-study post authorisation exposure

The first MA for NB as an adjunct to a reduced-calorie diet and increased physical activity was granted in the US on 10-Sep-2014 (international birth date [IBD]). NB (Contrave) was launched in the US in Oct-2014. On 26-Mar-2015, NB received MA via the centralised procedure (CAP) in the EU (Mysimba). NB (Mysimba) has been launched in the EU beginning in the 4th quarter of 2016. On 28-Apr-2016, NB received MA in South Korea. NB (Contrave) was launched in South Korea in Jun-2016. The product is currently authorised in the US, South Korea, Canada and all 28 countries in the EU, as well as European Economic Area (EEA) members Iceland, Liechtenstein, and Norway. Product launches are beginning within the Middle East, where Contrave recently became available in Lebanon.

Since this fixed combination product was introduced to the market (under the brand name Contrave®), as of June2018, approximately 2.3 million prescriptions have been written for the product (IMS data on file) in the U.S. As of the same date, based upon the number of tablets sold (MIDAS data on file) /112 tablets per pack, outside of the U.S., it is estimated that approximately 200,000 prescriptions have been written, with approximately 40% or 80,000 of these prescriptions occurring within the EEA where the product was launched beginning in the 4th quarter of 2016.

Post-authorisation use in population not studied in clinical trials

At the time of the update to this RMP, the product is being commercialized according to the indication studied in the clinical development programme in overweight (BMI: $\geqslant$ 27 kg/m^2 to < 30 kg/m^2) and obese (BMI: $\geqslant$ 30 kg/m^2) patients 18 years of age and older. While the MAH is aware of use in patients not meeting the BMI criteria or in patients less than 18 years of age, its use in these specific populations not studied in the development programme is extremely limited and is being monitored and assessed in periodic reporting. Based upon currently available information, a safety concern has not been identified.

Post-authorisation Off-label use

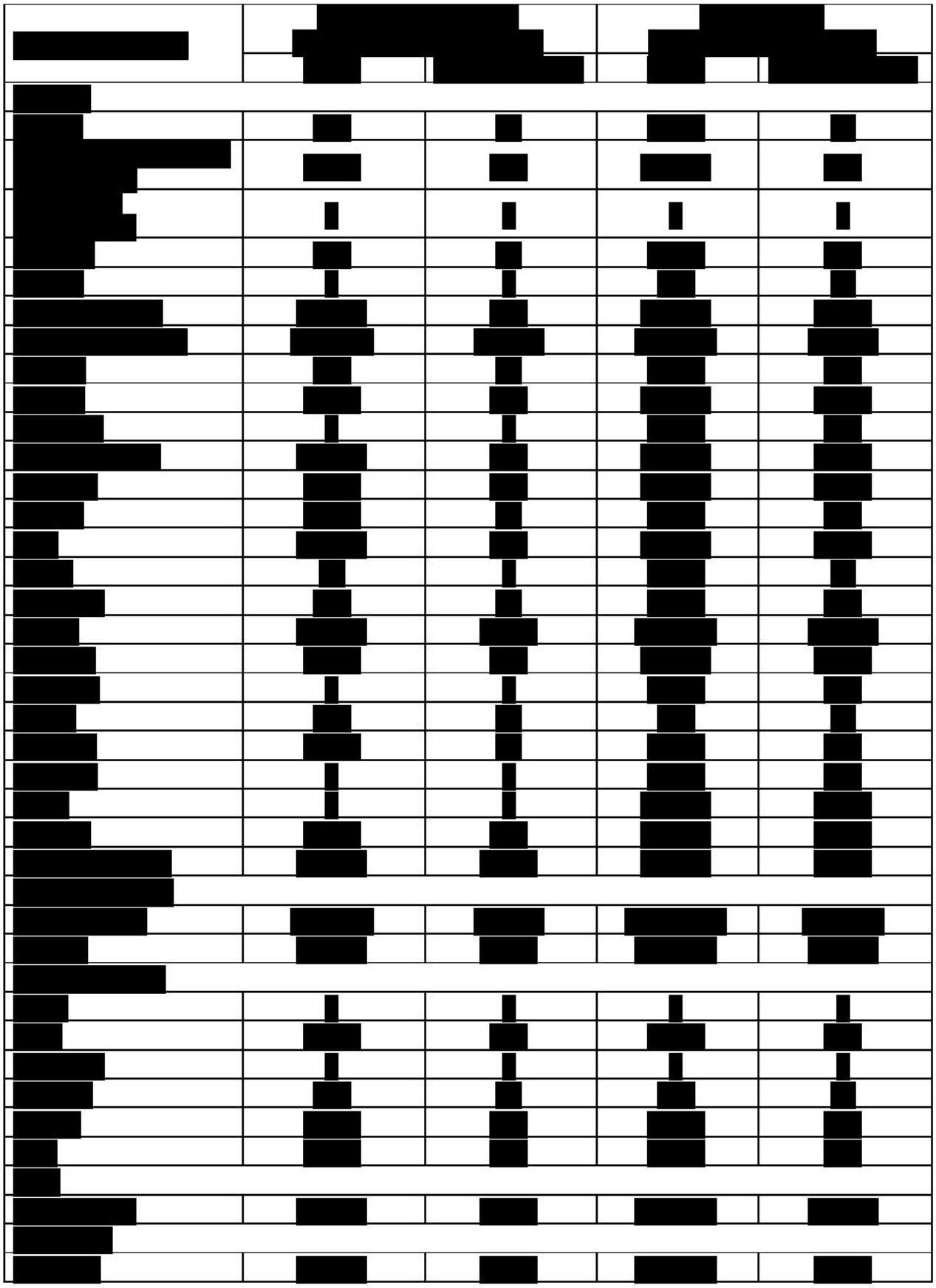
The MAH is aware of events of off-label use from post-marketing sources. Patterns of off-label use and abuse potential are being monitored and assessed in periodic reporting. Utilising data from Orexigen's global safety database through to 9th September, 2021, in total, there were 104 events of Off-label use and 32 events of Product use in unapproved Indication. In addition, there were a total of 113 events of Intentional product use issue reported primarily from PSPs in USA, Canada and Australia.Overall, based upon this currently available information in the context of the non-study post-authorization exposure described above in Section SV.2, a safety concern has not been identified. Further, the Physician Prescribing Checklist as described within this RMP is designed to assist prescribers in the EU to select patients in which this product's use is appropriate.

SV.1.1 Method used to calculate exposure

As per recommendations in the PRAC assessment of PBRER #2, methodology for calculating post-marketing exposure to NB in the previous PBRERs 3, 4, and 5 in patient-years was as follows: (the total number of sold tablets) / (4 tablets per day) / (365.25 days per year).

Based upon the business distribution model utilized in the marketing of Contrave/Mysimba worldwide and the method by which the business partners share sales/distribution data with the Company, a common method to estimate patient exposure has been employed using units sold. In some regions for example, the U.S. and Canada, the product is packaged in bottles; 120 tablets are present within a single unit. In other regions, for example the EEA countries, the product is packaged in blister packs; 112 tablets are present within a single unit. In order to calculate patient-years, a step was added to the formula utilized in the previous PBRER. To calculate the number of tablets, the number of units was multiplied by either 120 or 112, and then using the formula from previous PBRERs, that number of tablets was divided by 4 (number of tablets/day at the recommended dose) and then divided by 365.25 (days/year) in order to obtain the number of patient-years.

SV.1.2 Exposure



[redacted]	[redacted]	Cumulative (launch to 09Sep22)	
		Units	Patient-years
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
Total		**6,370,108**	**517,733**

Units = 120 tablet count bottles in the US, South Korea, Canada and Latin America; 112 tablet count blister packs elsewhere.

The summary of regional exposure may not equal the sum of the individual countries due to rounding of the calculated values

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

A review of the NB integrated safety datasets was conducted to evaluate potential signals of abuse or dependence potential in subjects treated with naltrexone HCl-bupropion HCl combinations which was evaluated for AE frequencies, deaths, treatment-emergent SAEs and cases of overdose. Analysis consistent with the *Abuse Potential Assessment and Scheduling Recommendation* (69) found no evidence of increased abuse or dependence potential in the NB clinical programme. There were no deaths or SAEs attributable to drug abuse or withdrawal, no overdoses, and evidence of drug diversion or inappropriate self-administration. A broad search of AEs for those potentially related to abuse or dependence potential yielded no findings in the core set of AEs of interest, and a small number of psychiatric and neurological events, most notably fatigue and somnolence. Therefore, the evidence gathered to date does not suggest that misuse for illegal purposes is a potential safety issue for NB.

Neither naltrexone HCl nor bupropion HCl, the individual components of NB, is associated with the potential for dependence. Both drugs are approved for the treatment of patients with addiction disorders (naltrexone HCl for opioids and alcohol, and bupropion HCl for nicotine).

Naltrexone HCl Historical Experience

Naltrexone HCl is a specific, high affinity, long acting opioid antagonist, which has negligible opioid activity. Tolerance does not develop with prolonged use (52). Reports of misuse of naltrexone HCl have been rare in the literature (70).

Bupropion HCl Historical Experience

The Wellbutrin XR® product information mentions that data in animals suggested a potential for abuse. However, studies on abuse liability in humans and extensive clinical experience show that bupropion HCl has low abuse potential (40), although there are anecdotal reports of recreational use and/or abuse of bupropion HCl in the literature. Articles describe inappropriate use of immediate release bupropion HCl by nasal insufflation or intravenous injection by subjects with a history of drug abuse for mild amphetamine-like effect (71,72).

The combination of the two components in a single fixed dose, sustained release formulation makes NB a distinctly different product with respect to this abuse potential than stand alone, immediate release bupropion. It is believed the potential for gastrointestinal side effects (primarily nausea) and the opioid antagonism contributed by the naltrexone component diminishes the sought-after effects of bupropion and therefore makes the abuse potential low.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Summary of safety concerns	
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 • Gastrointestinal disorders (nausea, vomiting)
Important potential risks	• Suicidality in patients with depression • Off-label use and abuse potential • Cholecystitis associated with rapid weight loss • Congenital malformations
Missing information	• Use during pregnancy • Use during breastfeeding/lactation • Effect on fertility • Use in paediatric patients • Data on long-term use /chronic use beyond 1 year • Use in patients with hepatic impairment • Use in patients with severe or moderate renal impairment

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

The following studies do not relate to any direct safety concern in the safety specification of NB and have been included here for completeness as they have been requested by other regulatory authorities for reasons not related to a specific safety concern. These represent areas of missing information where the objective was to investigate the possibility of a risk or provide reassurance about absence of a risk.

Thorough QT Study (NaltrexBuprop-1001): This study was conducted according to ICH E14 and is complete. This study demonstrated:

• NB had no effects on PR and QRS interval duration, QTc, or other electrocardiographic parameters.

• The validity of this study was demonstrated by the following:

- The moxifloxacin positive control group showed the expected QTc prolongation required to demonstrate assay sensitivity in the ICH E14 guidance as prospectively defined in the statistical plan.
- The placebo group's change from Baseline was small for QTcF and shows that the spontaneous factors for QTc change were well controlled.

• Based on a categorical outlier analysis, there was a lack of any effect of NB on heart rate, atrioventricular conduction, or cardiac depolarization as measured by the QRS duration.

• There were no new clinically relevant morphological T wave changes demonstrating a signal of concern on NB compared with placebo.

• There was no signal of any effect of NB or its metabolites on cardiac repolarization as evidenced by the results of the time-matched, outlier, and PK/PD analyses.

DDI Metformin Study (NaltrexBuprop- 1004)

The study is complete and has been previously submitted. This study demonstrated:

• Following single administration of metformin in the presence of NB, maximum exposure to metformin (C_{max}) was comparable to that observed with repeated administration of NB alone. However, overall exposure to metformin ($AUC\infty$ and AUC_t) was 23% higher in the presence of NB compared with metformin alone, and the corresponding upper bound of the 90% CI for the GMR fell above the predefined acceptance limit (80.00%, 125.00%). Therefore, relative bioavailability for metformin systemic exposure could not be demonstrated in healthy subjects, as a small increase in overall exposure was observed after metformin plus NB treatment.

• Following repeated administration of NB, administration of a single dose of metformin did not alter the systemic exposure to naltrexone, bupropion, and each of their metabolites compared with that observed with repeated administration of NB alone. Consequently, relative bioavailability was demonstrated.

• The effect of NB on metformin PK is likely due to a combination of effects on the OCT2 transporter and transient, mild effects on glomerular filtration.

List of Risks:

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers.

Gastrointestinal disorders (nausea, vomiting):

This is a known risk that does not impact the risk-benefit profile. There are no additional risk minimisation measures in place, no further evaluation or specific clinical actions foreseen, the risk is adequately addressed in the PI. As per PRAC recommendations, GI disorders has been removed from the list of safety concerns as important identified risk. Gastrointestinal disorders will continue to be monitored as part of the routine pharmacovigilance plan for NB namely through signal detection and adverse reaction reporting.

Cholecystitis associated with rapid weight loss:
This is a known risk that does not impact the risk-benefit profile. There are no additional risk minimisation measures in place, no further evaluation or specific clinical actions foreseen, the risk is adequately addressed in the PI. As per PRAC recommendations, Cholecystitis associated with rapid weight loss has been removed from the list of safety concerns as important potential risk. Cholecystitis associated with rapid weight loss will continue to be monitored as part of the routine pharmacovigilance plan for NB namely through signal detection and adverse reaction reporting.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

The active components of the fixed combination (naltrexone HCl and bupropion HCl) have been approved and marketed in Europe since 1984 and 1999, respectively, during which time over 500,000 patients have received naltrexone HCl and 10 million patients have received bupropion HCl. In the US, over 1 million and 50 million patients have received naltrexone HCl and bupropion HCl, respectively. Therefore, the risk (identified and potential) associated with the use of these products are well understood.

With respect to bupropion, as stated in the GlaxoSmithKline Module 1.8.2 European Union Risk Management Plan (https://laegemiddelstyrelsen.dk/upload/rmp/28103134700%2021-09-2017.pdf) and the Orion Corporation Public Summary of the Risk Management Plan (150mg and 300mg) tablets (https://www.fimea.fi/documents/160140/1204866/Bupropion+Orion+RMP+summary-EN.pdf/a27644a8-012a-48fa-ba8b-c944e5c8c59d), the following are risks (Identified and Potential) associated with this specific component of the fixed combination:

- Fits (seizures)
- Allergic reactions
- High blood pressure or increase in blood pressure
- Interactions

- Thoughts of suicide and worsening of depression
- Heart rhythm and electrical conduction disorder or irregular heartbeats
- Psychological effects and effects on the nerves when used to stop smoking
- Heart and blood vessel malformations in babies with maternal use during pregnancy

With respect to naltrexone, a public summary of the Risk Management Plan did not list any specific risks (https://laegemiddelstyrelsen.dk/upload/rmp/28104964511%2017-07-2017.pdf). However, the U.S.P.I. for REVIA (https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/018932s017lbl.pdf) specifies within the Warnings section a risk for hepatotoxicity. In addition, while it states no causal relationship has been established, REVIA too has a warning for depression and suicidality.

The published risks associated with the individual components form the basis for those deemed appropriate to include in this RMP for the fixed combination. The clinical trials for Mysimba did not identify any synergistic effects unique to the fixed combination, meaning that the risks identified consisted of those associated with the individual active ingredients as well as those identified to be associated with Mysimba specifically. Based upon this collective experience with the fixed combination and its individual active ingredients, the Important Identified and Potential Risk (and missing information) are those listed below:

Important Identified Risk

Important identified risks include:

- **Seizures:**

  additional RMM: physician prescribing checklist, PPC

  additional PhV activities: PASS NB-451 (drug utilisation and safety study), NB-452 (evaluation of the effectiveness of the PPC)

  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).

  NB will be supplied in blister packs which can help reduce the likelihood of medication dosing errors including overdose and the dose-related risk of seizures

- **Interaction with MAOIs, opioid analgesics, drugs that inhibit, induce or are substrates of CYP2B6, and drugs metabolised by CYP2D6:**

  additional RMM: PPC

  additional PhV activities: PASS NB-451, NB-452

- **Transient increase in blood pressure or heart rate:**

  additional RMM: PPC

  additional PhV activities: PASS NB-452 and NB CVOT 2.

  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.)

- **Hypersensitivity including severe reactions like Stevens-Johnson Syndrome:**

  additional PhV activities: PASS NB-451

- **Neuropsychiatric symptoms:**

  additional RMM: PPC

  additional PhV activities: PASS NB-451, PASS NB-452

- **Hepatotoxicity:**

  additional RMM: PPC

additional PhV activities: PASS NB-451, PASS NB-452

- **Use in patients with hepatic impairment:**
  additional PhV activities: None.
  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); contraindicated in patients with severe hepatic impairment (SmPC section 4.3); not recommended in patients with moderate hepatic impairment (SmPC sections 4.4 and 5.2).

- **Use in patients with severe or moderate renal impairment:**
  additional PhV activities: None.
  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 naltrexone/bupropion.
  Contraindicated in patients with end-stage renal failure (SmPC section 4.3).

The Risk benefit impact of the risks presenting the reasons for this classification, consider seriousness, frequency and severity are described in section SVII.3.1. Presentation of important identified risks and important potential risks, of the RMP.

Important Potential Risk

Important potential risks include:

- **Suicidality in patients with depression**

  additional RMM: PPC

  additional PhV activities: PASS NB-451, NB-452

  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.)

- **Off-label use and abuse potential**

  additional RMM: PPC

  additional PhV activities: PASS NB-451, NB-452

- **Congenital malformations*:***

  additional PhV activities: None.

The Risk benefit impact of the risks presenting the reasons for this classification, consider seriousness, frequency and severity are described in section SVII.3.1. Presentation of important identified risks and important potential risks, of the RMP.

Missing information

- **Use during pregnancy**:
  additional PhV activities: None.
- **Data on long-term use /chronic use beyond 1 year:**
  additional PhV activities: None.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk – SEIZURES	
MedDRA terms	Convulsions (SMQ) and HLGT Seizures (including subtypes): Convulsion, grand mal convulsion
Potential mechanisms	The potential mechanisms behind the putative association between NB and seizures are unknown. However, an increase in the risk of seizures can be attributed to the bupropion HCl component of NB due to the possible lowering of seizure threshold. Bupropion HCl historical experience: There is an increased risk of seizures occurring with the use of Zyban® in the presence of predisposing risk factors which lower the seizure threshold (77). Pharmacokinetic interactions have been attributed to an increased likelihood of seizures, as plasma levels of bupropion HCl or its metabolites may be altered which may increase the potential of seizures (77). It has been hypothesised that a gradual increase to peak plasma levels (Cmax) and fewer exposures over the course of 24 hours to spikes in peak plasma levels are responsible for the lower rate of seizures in the SR and XL formulations of bupropion HCl (82).
Evidence source(s) and strength of evidence	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 (C_{max} 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%.
Frequency with 95% CI	Among subjects treated with NB in phase 2/3 studies included in the primary integrated safety dataset, the *incidence risk* of seizures over the course of the NB clinical trial programme can be calculated as 0.06% (n=2/3,239). There were no cases of seizures in the placebo group. The attributable risk (AR) for seizures can be calculated as 0.06% - 0.00% = 0.06%. A relative risk (RR) cannot be calculated in the absence of unexposed cases. Two cases (n=2/4455; <0.1%) of seizure were reported in NB treated subjects in NB-CVOT. The seizure rate from this study is consistent with the rate reported in phase 3 programme and is no higher than the seizure rate with bupropion as a single agent at approved doses. Pisani *et al.* reported in a systematic review of patients treated with widely used antidepressants or antipsychotics applied at therapeutic doses that incidence risk of seizures have ranged from 0.1% to 1.5% (80). The incidence rate of seizures associated with *rimonabant* use have been reported 0.044 per 100 patient years, or approximately an incidence risk of 0.044% per year (81). Available evidence suggests that bupropion HCl at the currently approved dose of 300 mg/day has a seizure rate that is not

Important Identified Risk – SEIZURES	
	greater than that of other anti-depressant medications. Furthermore, the comparable PK profile between NB and commercially available doses of 300 mg/day bupropion HCl corroborates the observation of a seizure rate <0.1% in the NB phase 3 programme.
Severity and reversibility	In the phase 3 programme, in the NB treated group both seizure events (100%) were severe and none (0%) was fatal. The NB clinical trial programme excluded subjects with an active seizure disorder or those who had a predisposition to seizures including history of bulimia or anorexia nervosa, head trauma, and cerebrovascular accident. Nonetheless, 2 subjects in the NB clinical trial programme experienced seizures as a serious adverse event where one case experienced convulsion and the other had a grand mal convulsion. Both cases of seizures were single events that resolved without sequelae. One subject reported unobserved pre-syncope after the event and drug discontinuation, and the other had diabetes with a history of hypoglycaemia; the event details were suggestive of, but not conclusive for, hypoglycaemic seizure.
Seriousness/long term outcomes	No subjects in the placebo group experienced a serious or fatal event of seizure, as compared to the NB treated group where cases of seizures were considered to be *serious* and led to a discontinuation of therapy; subjects recovered without further complications.
Impact on quality of life	A review of the literature could not identify any published sources which measured the impact of single seizure episodes on HRQoL in the adult obese population.
Background incidence/prevalence	Population-based background incidence and prevalence of seizures in the untreated adult obese (target) population could not be identified in our review of the literature.
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 (80); therefore, seizure is an expected safety concern with bupropion HCl therapy that is highly dose-dependent (77). 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 (77). 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 (78,79). 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) (77). 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 (77). <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

Important Identified Risk – SEIZURES	
	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.
Preventability	The risk of seizures associated with NB exposure can be reduced through routine and additional risk minimisation activities including the PPC. NB is contraindicated in patients with risk factors for seizures or in risk groups known to be at an increased risk of seizures, including seizure disorder or a history of seizures, concomitant use of any other medication containing bupropion HCl, 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, or concomitant administration of monoamine oxidase inhibitors (MAOI) (NB SmPC Section 4.3). These risk factors are highlighted in the Physician Prescribing Checklist that is being implemented as a risk minimization tool. NB will be supplied in blister packs which can help reduce the likelihood of medication dosing errors including overdose and the dose-related risk of seizures. NB should be discontinued and not restarted in patients who experience a seizure while being treated with the medicinal product (NB SmPC Section 4.4).
Impact on the risk-benefit balance of the product	Based on the current available information on Mysimba, NB has been shown to be an effective treatment in obese and overweight patients receiving a range of behavioural modification, diet and exercise counselling. The occurrences of seizure analysed in the post marketing surveillance are consistent with the known pharmacologic profiles of the individual components (specifically the Bupropion component) and the fixed combination, as well as the guidance to the prescriber presented in the SmPC and other worldwide product labelling. To date, in the Global Safety Database there were no signals involving seizure related reports with a review of occurrences reported within this specific risk revealing no factors (individually or in aggregate) that would be indicative of a previously unknown or emerging safety issue. The risk of seizures associated with NB exposure can be reduced through routine and additional risk minimisation activities. NB is contraindicated in patients with risk factors for seizures or in risk groups known to be at an increased risk of seizures including seizure disorder or a history of seizures, concomitant use of any other medication containing bupropion hydrochloride, 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 or concomitant administration of MAOI (NB SmPC Section 4.3). These risk factors are also highlighted in the Physician Prescribing Checklist (PPC) that has been implemented as a risk minimisation tool. NB is supplied in blister packs which can help reduce the likelihood of medication dosing errors including overdose and the dose-related risk of seizures. NB should be discontinued and not restarted in patients who experience a seizure while being treated with the product (NB SmPC Section 4.4). Overall, this risk is manageable through proper patient selection, adherence to SmPC warnings and precautions instructions, further an important aspect of the PPC will be educating prescribers on the importance of appropriate patient selection and clinical management. Occurrences of seizure will continue to be monitored as part of the routine PV plan for NB. The benefit-risk profile for Mysimba® remains favourable.
Public health impact	The potential public health impact of seizures with NB use is expected to be minimal given the small number of cases in the NB clinical trials programme and the absence of serious outcomes resulting from the seizures (subjects recovered without further complications). The potential public health impact of seizures can be estimated using number needed to harm (NNH) (83). The NNH for seizures in the NB phase 2/3 clinical trial programme can be

Important Identified Risk – SEIZURES	
	calculated by taking the inverse of the attributable risk (AR): 1/AR = 1/0.0006 = 1,667). Therefore, approximately 1,667 obese adults would need to be treated with NB before observing 1 treatment-emergent case of seizure assuming a causal relationship between NB and seizures.
Reference source	(77) Zyban SmPC 2018 (78) Dunner DL et al. 1998 (79) Johnston JA et al. 1991 (80) Pisani et al. 2002 (81) Zimulti FDA briefing document 2007 (82) Jefferson JW et al. 2008 (83) Citrome L et al. 2010

Important Identified Risk – INTERACTION WITH MAOIS, OPIOIDS, DRUGS THAT INHIBIT, INDUCE OR ARE SUBSTRATES OF CYP2B6, AND DRUGS METABOLISED BY CYP2D6

Overview of potential for interactions

There is significant information on the drug-drug interaction (DDI) potential of NB based on NB studies or published information on the individual constituents. Interactions tested in the NB clinical pharmacology studies included: atorvastatin; valsartan; glyburide; nifedipine; lisinopril and metoprolol. Key findings are as follows:

- There is no significant interaction between the bupropion and naltrexone components of the fixed drug combination NB in terms of pharmacokinetic interactions (study NB-230), exaggerated primary pharmacodynamic interactions (of toxicologic relevance) or secondary PD interactions, toxicologic interactions, and/or competition for or alteration of the activity or endogenous levels of the same enzymes or other intracellular molecules.
- From the Pharmacokinetic Drug Interaction Studies conducted as part of the NB Clinical Pharmacology Programme, assessing Effect of Naltrexone and/or Bupropion on Other Agents or of Other Agent(s) on Naltrexone and/or Bupropion, it was concluded that NB increased the AUC and C_{max} of metoprolol; metoprolol reduced AUC and C_{max} of naltrexone but had no effect on bupropion; glyburide reduced AUC and C_{max} of both bupropion and naltrexone; and, nifedipine decreased AUC and C_{max} of naltrexone and C_{max} of bupropion. Increased naltrexone exposures in these studies are not expected to be clinically meaningful.
- A drug-drug interaction study (NaltrexBuprop-1004) involving NB and the concomitant use of metformin has been conducted. This study demonstrated the following results:
- Following single administration of metformin in the presence of NB, maximum exposure to metformin (Cmax) was comparable to that observed with repeated administration of NB alone. However, overall exposure to metformin (AUC_∞ and AUCt) was 23% higher in the presence of NB compared with metformin alone, and the corresponding upper bound of the 90% CI for the GMR fell above the predefined acceptance limit (80.00%, 125.00%). Therefore, in healthy subjects, a small increase in overall exposure was observed after metformin plus NB treatment.
- Following repeated administration of NB, administration of a single dose of metformin did not alter the systemic exposure to naltrexone, bupropion, and each of their metabolites compared with that observed with repeated administration of NB alone. Consequently, relative bioavailability was demonstrated.
- The effect of NB on metformin PK is likely due to a combination of effects on the OCT2 transporter and transient, mild effects on glomerular filtration. These observations are not considered to be clinically relevant.
- No PK interaction between atorvastatin and NB was observed. No safety signal of rhabdomyolysis was raised during the NB phase 2/3 clinical development program. In the NB-CVOT study, 88% of subjects were on pharmacotherapy for dyslipidaemia, 80% subjects received concurrent statins. There were no reports of rhabdomyolysis in NB treated subjects.
- In vitro studies have confirmed that naltrexone HCl does not have the potential to inhibit or induce cytochrome P450 (CYP) enzymes and has no known PK drug-drug interactions (aside from changes attributed to the effect of food) (42,43).

- Co-administration of NB with drugs that are metabolised by the CYP2D6 isozyme should be approached with caution as bupropion HCl can increase the PK concentrations of CYP2D6 substrates by non-competitive inhibition (44–46).
- Co-administration of drugs that induce the metabolism of bupropion HCl and its metabolites (e.g., carbamazepine, lopinavir, rifampin) may lead to potentially reduced efficacy of NB (113–118).
- Metabolic inhibition of CYP2B6 is unlikely to result in clinically meaningful effects on bupropion HCl due to the multiple metabolic pathways of bupropion HCl (119,120). Bupropion HCl and its active metabolites inhibit in vitro metformin uptake in cells expressing human OCT2. NB co-administration could result in increased exposure of metformin or other OCT2 substrates (e.g. pindolol, ranitidine and varenicline in a manner similar to cimetidine) (121–123).
- Limited clinical data suggest a higher incidence of adverse effects (e.g. neuropsychiatric events) in patients receiving bupropion HCl concurrently with either levodopa or amantadine (124). No studies were conducted with NB and levodopa or amantadine.
- Although no DDI study has been conducted with NB administered in combination with psychotropic agents like antidepressants, bupropion has been used for augmentation of SSRI antidepressant therapy, where it has been generally well tolerated and associated with improvement in depressive symptoms (125–127). Information available from the NB-CVOT study demonstrated 23.1% of subjects enrolled into the study were using antidepressant agents (amongst which 15.4% were using SSRIs). Subjects using antidepressants did not exhibit unique safety concerns.
- Food effect: the PK of bupropion and naltrexone when NB was administered as a single dose shortly after a meal was examined in Studies NB-233, NB-236 and NB-239, and at steady state in Study NB-236. The effect of food on exposure of bupropion and its metabolites were minor, especially with moderate meals or at steady state, and unlikely to be of clinical significance. Food may be expected to increase exposure to naltrexone, but the inter-individual variations in the size of the effect should not present a safety or efficacy concern given the overlapping distribution in exposures, due to the typically high variability in naltrexone exposure. The food effect observed with NB is not expected to substantially impact the efficacy or safety of the drug, relative to administration without food. In Study NB-CVOT, subjects were not instructed to take NB with food, and both the observed efficacy and safety profiles are consistent with the observations from Phase 3. The SmPC includes relevant text in Section 5.2 and Section 4.2, and in Section 4.5 states that the tablets "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".

Study	Parameter	Analyte	Comparison to Fasted State		Comparison of High-Fat to Moderate Fat
			Moderate-Fat	High-Fat	
NB-233	C_{max} (ng/mL)	Naltrexone	N/A	370.57%	N/A
		Bupropion		179.74%	
	$AUC_{0-\infty}$ (ng·hr/mL)	Naltrexone		207.01%	
		Bupropion		138.25%	
NB-237/ NB-239[a]	C_{max} (ng/mL)	Naltrexone	213.71%	N/A	N/A
		Bupropion	98.75%		
	$AUC_{0-\infty}$ (ng·hr/mL)	Naltrexone	180.23%		
		Bupropion	92.60%		
NB-236	C_{max} (ng/mL)	Naltrexone	180.53%	191.64%	105.17%
		Bupropion	117.20%	127.97%	109.47%
	AUC_{0-12} (ng·hr/mL)	Naltrexone	169.70%	169.97%	100.20%
		Bupropion	109.70%	111.94%	102.53%

Abbreviations: High-Fat=high-calorie, high-fat prandial state; Moderate-Fat=moderate-calorie, moderate-fat prandial state [a] Fed state in Study NB-239 was compared to fasted state for NB 8/90 tablets in Study NB-237 Note: Shaded cells indicate that the 90% CI fell within the 80 to 125% bioequivalence range.

Important identified risks associated with specific drug interactions are presented below:

Interacting substance(s)	**MONOAMINE OXIDASE INHIBITORS (MAOIs)**
MedDRA terms (PT)	Drug interaction
Potential mechanisms	The potential for pharmacological interaction can occur because both MAOIs and bupropion increase the bioavailability of NE and DA ((77), (121)). Whereas monoamine oxidase A (MAO-A) preferentially deaminates serotonin, melatonin, epinephrine, and norepinephrine, MAO-B preferentially deaminates phenylethylamine and trace amines. Dopamine is equally deaminated by both types. While some new MAOIs are selective, older MAOIs are non-selective and irreversible (128). Both MAOIs and bupropion HCl enhance catecholamines by inhibiting reuptake of norepinephrine (NE) and dopamine (DA), albeit by different mechanisms (77), (128). The concomitant use of an MAOI with bupropion HCl could theoretically increase the levels of norepinephrine and dopamine, which could exaggerate the effects or prolong the effects of NB.
Evidence source(s) and strength of evidence	Since monoamine oxidase A and B inhibitors also enhance the catecholaminergic pathways by inhibiting reuptake of norepinephrine and dopamine, by different mechanisms, the concomitant use of an MAOI with bupropion HCl could theoretically increase the levels of norepinephrine and dopamine, which could exaggerate the effects or prolong the effects of NB and pose a health risk to patients, including an increased risk of seizure, agitation, or hypertensive crisis. Concomitant use of NB and monoamine oxidase inhibitors (MAOIs) is contraindicated as there is an increased possibility of adverse reactions from their co-administration.
Frequency (with 95 % CI)	Of the cumulative drug-drug interaction (DDI) events, there have been no events associated with a definitive interaction between NB and MAOIs.
Severity and reversibility	Cumulatively, there have been no DDI events associated with an interaction between NB and MAOIs. The nature of this risk is determined by the mechanisms of action of MAOIs and bupropion. The resulting increase in both norepinephrine and dopamine can potentially lead to seizures, agitation and severe increases in blood pressure which has not been reported from spontaneous sources or PSP nor observed in clinical trials with NB.
Seriousness/ long term outcomes	Cumulatively, there have been no DDI events associated with a definitive interaction between NB and MAOIs.

Interacting substance(s)	**MONOAMINE OXIDASE INHIBITORS (MAOIs)**
Impact on Quality of life	Elevated levels of norepinephrine or dopamine stemming from an interaction between MAOIs and NB can theoretically pose a health risk to patients, including an increased risk of seizure, agitation, or hypertensive crisis. Since monoamine oxidase A and B inhibitors also enhance the catecholaminergic pathways, by a different mechanism from bupropion, NB must not be used with MAOI (NB SmPC Section 4.5).
Risk factors and risk groups	Obese patients requiring treatment with MAOIs for co-morbidities such as depression, anxiety disorders, personality disorders and Parkinson's disease such as phenelzine, selegiline, or rasagiline. The high incidence of obesity combined with the need for weight management and treatment of these co-morbidities make it likely that patients will receive both MAOIs and NB (Mysimba) if the product information of Mysimba is not adhered to.
Preventability	NB is contraindicated in patients who take MAOIs and the SmPC recommends that at least 14 days should elapse between discontinuation of MAOI and initiation of treatment with NB (NB SmPC Section 4.3 and Section 4.5).
Impact on the risk-benefit balance of the product	Cumulatively, in the global safety database, there have been no drug-drug interaction (DDI) events associated with an interaction between NB and MAOIs, there were no signals involving interactions or worsening of outcomes of known interactions, with a review of occurrences of "interactions" reported revealing no factors (individually or in aggregate) that would be indicative of a previously unknown or emerging safety issue. This risk can be reduced through routine and additional risk minimisation activities. NB is contraindicated in patients who take MAOIs and the SmPC recommends that at least 14 days should elapse between discontinuation of MAOI and initiation of treatment with NB (NB SmPC Section 4.3 and Section 4.5), in addition an important aspect of the PPC will be educating prescribers on the importance of appropriate patient selection and clinical management. The analysis of cumulative data regarding DDIs will continue to be monitored as part of the routine PV plan for NB and during routine monthly signalling activities. Cumulative data support a positive benefit-risk profile for NB and no new safety concern has been identified. The benefit/risk balance for Mysimba™ remains favourable.
Public health impact	Co-morbidities of obese patients include depression, anxiety disorders, personality disorders and obsessive-compulsive disorders. MAOIs are used to treat these conditions. The high incidence of obesity combined with the need for weight management and treatment of these co-morbidities make it likely that patients will receive both MAOIs and NB (Mysimba) if the product information of NB (Mysimba) is not adhered to. This applies also to NB marketed as NB (Contrave) in the US (NICE 2014). Elevated levels of norepinephrine or dopamine stemming from an interaction between MAOIs and NB can theoretically pose a health risk to patients, including an increased risk of seizure, agitation, or hypertensive crisis. Since monoamine oxidase A and B inhibitors also enhance the catecholaminergic pathways, by a different mechanism from bupropion, NB must not be used with MAOI (NB SmPC Section 4.5). The public health impact is expected to be minimal to moderate depending on awareness of the potential interaction between MAOIs and NB and its consequences and adherence to the product information.
Reference Source	(77) Zyban SmPC 2018 (128) Yildiz A et al. 2002 (121) Wellbutrin prescribing information 2013

Interacting substance(s)	**OPIOIDS**
MedDRA terms (PT)	Drug interaction
Potential Mechanisms	The primary pharmacology of naltrexone is competitive blockade of opioid receptors. Naltrexone binds with very high affinity to the mu subtype but also has substantial affinity for kappa and delta receptors. It is believed that the blockade of

Interacting substance(s)	**OPIOIDS**
	physiological, subjective and reinforcing effects of opioids by naltrexone is primarily due to its effects at the mu receptor subtype. In vitro, naltrexone reverses the inhibition of adenylate cyclase produced by opioid agonists. Naltrexone is not known to have significant intrinsic efficacy as functional agonist or as an inverse agonist. *In vivo*, naltrexone and its metabolite 6β-naltrexol reverse opioid agonist effects on nociception and induce withdrawal in opioid-dependent animals (129–131). As measured by reversal of morphine's acute effect on nociception or locomotor activity, 6β-naltrexol is substantially less potent than naltrexone HCl, but in vivo, circulates at much higher concentrations and is effective when administered either centrally or peripherally (130). Despite its lower potency as an antagonist, 6β-naltrexol produces a longer lasting blockade than naltrexone HCl of the antinociceptive effects of morphine (130,132).
Evidence source(s) and strength of evidence	Due to the antagonistic effects of naltrexone at the opioid receptor, the primary effect of the interaction between opioid analgesics and NB would be a reduction of effect of the opioid analgesic therapy leading to lack or insufficient pain relief as NB may interfere with the treatment benefit from opioid-containing medicines such as strong painkillers (opioid–containing painkillers). A second potential effect of the interaction, in patients who are chronically using opioid-containing medications when they initiate therapy with NB, would be the precipitation of acute opioid withdrawal symptoms. 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.
Frequency (with 95 % CI)	While the NB clinical trials included exclusion criteria related to chronic use of opioid and opioid medications were not to be used during the trials, approximately 12% of both NB and placebo subjects took a concomitant opioid while enrolled in NB clinical studies. The majority of these subjects (~7% of the Total NB and placebo populations) continued study treatment while taking opioid or opioid-like medications. Frequent AEs experienced following the start of the opioid were similar between NB and placebo groups and were most commonly related to the concurrent disorder being treated (surgical and dental procedures, injuries, and respiratory and other infections) or to gastrointestinal symptoms such as nausea that are seen with both NB and opioids. In general, pain and constipation did not appear to be more frequent in subjects receiving NB, while nausea and vomiting appeared to be more frequent in subjects receiving NB with an opioid medication. There were no reports of respiratory depression, sedation or somnolence. In the post-marketing setting, cumulative reporting rates of co-administration of NB with opioids are 0.07 per 100 patient years outside the EEA and 0.02 per 100 patient years in the EEA.
Severity and reversibility	The nature of this risk is determined by the mechanism of action of naltrexone on opioid receptors. Due to competitive receptor inhibition, opioids are blocked from binding to these receptors by naltrexone. The result is a reduced opioid effect which may lead to lack of sufficient pain relief in opioid users or to withdrawal symptoms in opioid-dependent patients. Serious life-threatening reactions, such as seizure and serotonin syndrome, have been observed after co-administration of naltrexone/bupropion and opioids.
Seriousness/ Long term outcomes	While the NB clinical trials employed exclusion criteria related to chronic use of opioid, and opioid medications were not to be used during the trials, approximately 12% of both NB and placebo subjects took a concomitant opioid while enrolled in NB clinical studies. The majority of these subjects (~7% of the Total NB and placebo populations) continued study treatment while taking opioid or opioid-like medications. Frequent AEs experienced following the start of the opioid were similar between NB and placebo groups and were most commonly related to the concurrent disorder being treated (surgical and dental procedures, injuries, and respiratory and other infections) or to gastrointestinal symptoms such as nausea

Interacting substance(s)	**OPIOIDS**
	that are seen with both NB and opioids. In general, pain and constipation did not appear to be more frequent in subjects receiving NB, while nausea and vomiting appeared to be more frequent in subjects receiving NB with an opioid medication. There were no reports of respiratory depression, sedation or somnolence. None of the clinical trial cases where there was reported the concomitant use of NB and an opioid containing product reported with fatal outcome related to NB. While not often documented in the case file, due to the pharmacologic properties, the events will resolve with the discontinued use of either NB or the opioid containing product. When these cases are classified as serious, the patient has experienced withdrawal symptoms requiring a visit to the ER. In the post-marketing context, serious life-threatening reactions, such as seizure and serotonin syndrome, have been observed after co-administration of naltrexone/bupropion and opioids. Additionally, insufficient intra-/post-operative opioid analgesia during treatment with naltrexone/bupropion has been reported.
Impact on quality of life	Due to the antagonistic effects of naltrexone at the opioid receptor, the primary effect of the interaction between opioid analgesics and NB would be a reduction of effect of the opioid analgesic. A second potential effect of the interaction, in patients who are chronically using opioid-containing medications when they initiate therapy with NB, would be the precipitation of acute opioid withdrawal symptoms. In the post-marketing context, serious life-threatening reactions, such as seizure and serotonin syndrome, have been observed after co-administration of naltrexone/bupropion and opioids. Additionally, insufficient intra-/post-operative opioid analgesia during treatment with naltrexone/bupropion has been reported. The mu opioid antagonist naltrexone can reduce the effectiveness of opioid therapy. 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. Opioid-dependent persons are at risk of withdrawal symptoms when taking NB. This may negatively impact replacement therapy of these patients when they receive methadone. Attempts to overcome any naltrexone opioid blockade by administering large amounts of exogenous opioids can be very dangerous and may lead to a fatal overdose or life endangering opioid intoxication (e.g., respiratory arrest, circulatory collapse). Patients should be aware that they may be more sensitive to lower doses of opioids after NB treatment is discontinued.
Risk factors and risk groups	Obese patients requiring treatment with opioids, for example for pain relief (including risk of insufficient intra-/post-operative opioid analgesia), and patients with opioid dependence.
Preventability	Adherence to the NB SmPC Sections 4.3, 4.4 and 4.5 as well as associated text in PL. NB 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. NB 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 NB. If opioid therapy is required after treatment initiation, NB treatment must be stopped. In patients requiring intermittent treatment with opioids (e.g., due to a, surgical procedure), NB therapy should be discontinued for a minimum of 3 days before and the opioid dose should not be increased above the standard dose.

Interacting substance(s)	**OPIOIDS**
Impact on the risk-benefit balance of the product	Due to the antagonistic effects of naltrexone at the opioid receptor, the primary effect of the interaction between opioid analgesics and NB would be a reduction of effect of the opioid analgesic. A second potential effect of the interaction, in patients who are chronically using opioid-containing medications when they initiate therapy with NB, would be the precipitation of acute opioid withdrawal symptoms. In the Global safety database, there have been reports of patients receiving opioid treatment while under NB therapy, or starting NB while receiving opioid treatment for pain, who experienced diminished effect of pain medication (including insufficient intra-/post-operative analgesia). As a consequence, their pain control was suboptimal for up to several days. Some patients starting NB while taking an opioid treatment experienced characteristic AEs associated with withdrawal upon initiation of NB therapy. This spectrum of AEs is mechanistically consistent with this known drug-drug interaction. Further, serious life-threatening reactions, such as seizure and serotonin syndrome have been observed after co-administration of naltrexone/bupropion and opioids. Appropriate text is already included as a contraindication in the NB product label (NB SmPC Section 4.3, with additional text in Section 4.4 and Section 4.5). The risk of DDI between opioid therapy and NB exposure can be reduced and is manageable through proper patient selection and adherence to the SmPC. The PPC will also guide physicians to prescribe Mysimba appropriately. Routine pharmacovigilance monitoring with targeted surveillance and data collection for events of interest, allow the MAH to monitor for and manage any unforeseen risks that could potentially occur or any emerging safety issue. Cumulative data support a positive benefit-risk profile for NB. The risk benefit profile of Mysimba is considered favourable.
Public health impact	Co-morbidities of obese patients may include conditions requiring treatment with opioids, for example for pain relief. Intermittent excessive sugar intake may cause endorphin dependence as evidenced by signs of withdrawal upon opioid antagonist administration in an animal model (Colantuini, 2002). The public health impact is expected to be moderate due to the high incidence of obesity and significant incidence of opioid dependency. The naltrexone component of NB may cause withdrawal symptoms with potentially life-threatening consequences.
Reference Source	(129) Bhargava HN et al. 1994 (130) Raehal KM et al. 2005 (131) Divin MF et al. 2008 (132) Porter et al. 2002

Interacting substance(s)	**DRUGS METABOLISED BY CYTOCHROME P450 ENZYMES**
MedDRA terms (PT)	Drug interaction
Potential mechanisms	As bupropion is primarily metabolised to its primary metabolite, hydroxybupropion, by the CYP2B6 isozyme, medicinal agents that increase the activity of this isozyme will tend to decrease bupropion concentrations and increase hydroxybupropion concentrations, while medicinal agents that decrease the activity of CYP2B6 will tend to increase bupropion concentrations and decrease hydroxybupropion concentrations. Bupropion has several additional metabolic pathways other than CYP 2B6, and the pharmacological activity of bupropion is partly due to its active metabolites. Therefore, the potential for clinically meaningful effects of CYP 2B6 induction or inhibition on bupropion metabolism is low. The in vivo inhibition of CYP2D6 likely reflects the combined effects of bupropion and hydroxybupropion, which are relatively weak inhibitors, coupled with effects from the more potent inhibitors, erythrohydrobupropion and threohydrobupropion. Naltrexone is not subject to oxidative metabolism by cytochrome P450 isozymes. In the NB studies to assess potential DDIs, significant changes in naltrexone HCl or bupropion HCl PK were observed only in the glyburide and nifedipine investigations.

Interacting substance(s)	DRUGS METABOLISED BY CYTOCHROME P450 ENZYMES
	Increased naltrexone HCl exposures in these studies appear to be consistent with, and within the range of, those observed when NB tablets are administered with food and are not believed to be clinically meaningful. Based on approved product information and published clinical studies, bupropion is known to be metabolized to its major metabolite by the cytochrome P450 CYP2B6 and therefore inducers or inhibitors of CYP2B6 may affect bupropion PK. The potential exists for a drug interaction between NB and drugs that inhibit CYP2B6 isozyme (orphenadrine, ticlopidine, and clopidogrel). Compounds which inhibit the hydroxylation of bupropion in vitro include paroxetine, sertraline, norfluoxetine, fluvoxamine, nelfinavir, ritonavir and efavirenz. Clinical studies with ticlopidine have shown the greatest inhibition of bupropion metabolism, resulting in increased bupropion AUC and Cmax of 85% and 38%, respectively and decreased hydroxybupropion AUC and Cmax of 84% and 78%, respectively. Similar, but slightly smaller effects on the metabolism of bupropion were seen with clopidogrel and the hormone replacement therapy combination of estradiol valerate and levonorgestrel. Prasugrel was shown to produce small increases of 18% to bupropion AUC and decreases of 23% and 32% to hydroxybupropion AUC and Cmax, respectively. In contrast, the oral contraceptive combination ethinyl estradiol/desogestrel was shown to decrease AUC of both bupropion and hydroxybupropion. However, because bupropion HCl is metabolised by pathways in addition to CYP2B6 hydroxylation, the potential for clinically meaningful effects of CYP2B6 induction or inhibition is considered low. Based on approved product information and on a study designed to assess the effects of NB tablets on metoprolol exposure, bupropion and its metabolite hydroxybupropion have the potential to increase exposure of CYP2D6 substrates. In a clinical study, NB was co-administered with the CYP2D6 substrate metoprolol, and NB increased metoprolol AUC and Cmax by approximately 4- and 2-fold, relative to metoprolol alone. Similar clinical drug interactions resulting in increased PK exposure have been observed with bupropion as a single agent with desipramine and venlafaxine. Naltrexone is not subject to oxidative metabolism by CYP P450 isozymes, and thus there is little likelihood of PK interactions with CYP inhibitors or inducers.
Evidence source(s) and strength of evidence	Bupropion HCl is metabolised to its major active metabolite hydroxybupropion primarily by the cytochrome P450 CYP2B6. Co-administration of medicinal products that may affect 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. Co-administration of bupropion with drugs that are metabolised by CYP2D6 isozyme including certain antidepressants (SSRIs and many tricyclics, 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 medication.
Frequency (with 95 % CI)	Overall, definitive evidence that an event was associated with an interaction between NB and a concomitant medication metabolised by cytochrome P450 (DDIs) is lacking, where a report stating an interaction is only a suspicion. The analysis of cumulative data regarding DDIs will continue to be monitored in routine monthly signaling activities.
Severity and reversibility	Since bupropion is extensively metabolised, caution is advised when NB is co-administered with medicinal products known to induce CYP2B6 (e.g., carbamazepine, phenytoin, ritonavir, efavirenz) as these may affect the clinical efficacy of NB. Since bupropion hydrochloride is extensively metabolised, caution is advised when NB is co-administered with medicinal products known to inhibit metabolism (e.g., valproate) as these may affect its clinical efficacy and safety (NB SmPC Section 4.5).
Seriousness/ Long term outcomes	Overall, definitive evidence that an event was associated with an interaction between NB and a concomitant medication metabolised by cytochrome P450 (DDIs)

Interacting substance(s)	**DRUGS METABOLISED BY CYTOCHROME P450 ENZYMES**
	is lacking. The analysis of cumulative data regarding DDIs will continue to be monitored in routine monthly signaling activities.
Impact on quality of life	Bupropion hydrochloride is metabolised by pathways in addition to CYP2B6 hydroxylation. Hence, the potential for clinically meaningful effects of CYP2B6 induction or inhibition is considered low. Co-administration of bupropion with drugs that are metabolised by CYP2D6 isozyme including certain antidepressants (SSRIs and many tricyclics, e.g., desipramine, imipramine, paroxetine), antipsychotics (e.g., haloperidol, risperidone and thioridazine), betablockers (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 medication. Although citalopram is not primarily metabolised by CYP2D6, in 1 study, bupropion increased the C_{max} and AUC of citalopram by 30% and 40%, respectively. 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 NB 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 medication should be considered, particularly for those concomitant medications with a narrow therapeutic index. When feasible, the option of therapeutic drug monitoring should be considered for medicines with a narrow therapeutic index, such as tricyclic antidepressants.
Risk factors and risk groups	Obese patients requiring treatment for co-morbidities such as depression, other psychiatric disorders and conditions requiring beta blockers and antiarrhythmics treatments. In addition, bupropion has a dose-related propensity to cause 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%. Obese patients taking concomitant administration of medicinal products that may lower the seizure threshold, such as antipsychotics, antidepressants, antimalarials, tramadol, theophylline, systemic steroids, quinolones and sedating antihistamines as these combinations may increase the risk of seizures. The high incidence of obesity combined with the need for weight management and treatment of these conditions make it likely that patients will receive both drugs interacting with and being impacted by cytochrome P 450 enzymes and NB (Mysimba) if the product information of NB is not adhered to.
Preventability	NB is contraindicated in patients who take MAOIs and the SmPC recommends that at least 14 days should elapse between discontinuation of MAOI and initiation of treatment with NB (NB SmPC Section 4.3). 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. Because bupropion HCl is extensively metabolised, the co-administration of other drugs known to induce metabolism (e.g. carbamazepine, phenytoin, ritonavir, efavirenz) or inhibit metabolism (e.g. valproate) may affect its clinical efficacy and safety (NB SmPC Section 4.5).
Potential Health Risks	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. Because bupropion HCl is extensively metabolised, the co-administration of other drugs known to induce metabolism (e.g. carbamazepine, phenytoin, ritonavir, efavirenz) or inhibit metabolism (e.g. valproate) may affect its clinical efficacy and safety (NB SmPC Section 4.5). Bupropion is metabolised to its major active metabolite hydroxybupropion primarily by the cytochrome P450 CYP2B6. Co-administration of medicinal products that may affect 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 (77). However, as bupropion is also metabolised by other pathways, in addition to CYP2B6 hydroxylation, the potential

Interacting substance(s)	DRUGS METABOLISED BY CYTOCHROME P450 ENZYMES
	for clinically meaningful effects of CYP2B6 induction or inhibition on bupropion HCl exposure is considered low (119,120). Co-administration of bupropion with drugs that are metabolised by CYP2D6 isozyme including certain antidepressants (SSRIs and many tricyclics, 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 medication. 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. The potential health risks for this type of interaction would be predicted to be those related to excessive dosing with each of those agents. If NB 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 medication should be considered, particularly for those concomitant medications with a narrow therapeutic index. When feasible, the option of therapeutic drug monitoring (TDM) should be considered for medicines with a narrow therapeutic index, such as tricyclic antidepressants. 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. Naltrexone is not subject to oxidative metabolism by CYP isoforms and does not induce or inhibit CYP isoforms, therefore interactions based on CYP induction or inhibition are not considered likely (52).
Impact on the risk-benefit balance of the product	No interaction with drugs metabolised by cytochrome P450 enzymes was reported in the Global Safety Database and during postmarketing surveillance. Overall, definitive evidence that an event was associated with an interaction between NB and a concomitant medication metabolised by cytochrome P450 (DDIs) is lacking. 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. Coadministration of NB with drugs that are metabolised by CYP2D6 isoenzyme should be approached with caution and should be initiated at the lower end of the dose range of the concomitant medicinal product. Section 4.5 of the SmPC states that concomitant administration of NB with certain antidepressants should be approached with caution, such as Cymbalta which inhibits reuptake of serotonin and norepinephrine and undergoes predominately hepatic metabolism via 2 cytochrome P450 isozymes, CYP2D6 and CYP1A2. This risk can be reduced through routine and additional risk minimisation activities. Recommendations and precautions to be followed by healthcare professionals and patients for the safe and effective use of Mysimba have been included in the summary of product characteristics and the package leaflet. The analysis of cumulative data regarding DDIs will continue to be monitored in routine monthly signalling activities and postmarketing surveillance. The risk benefit balance of Mysimba remains favourable.
Public health impact	The high incidence of obesity combined with the need for weight management and treatment of co-morbidities typically observed in these patients including depression and other psychiatric disorders make it likely that patients will receive both drugs interacting with and being impacted by cytochrome p450 enzymes and NB (Mysimba) if the product information of NB (Mysimba) is not adhered to. This applies also to NB marketed as NB (Contrave) in the US. The public health impact is expected to be minimal to moderate depending on awareness of the potential interaction between drugs metabolised by or impacting cytochrome P450 enzymes and NB, the resulting consequences and the adherence to the product information.
Reference Source	(52) Nalorex SmPC 2018; (77) Zyban® SmPC 2018;

Interacting substance(s)	**DRUGS METABOLISED BY CYTOCHROME P450 ENZYMES**
	(119) Xu C et al. 2012; (120) Molnari JC et al. 2012; (133) Reese et al. 2008

Important Identified Risk –INCREASES IN BLOOD PRESSURE OR HEART RATE	
MedDRA terms	Hypertension (SMQ) Arrhythmia (SMQ) Tachyarrhythmia (SMQ)
Potential mechanisms	Bupropion HCl, by virtue of its effects, as a relatively weak dopamine and norepinephrine reuptake inhibitor, has sympathomimetic properties, and its observed haemodynamic profile has been well established and is described in the bupropion HCl prescribing information. As a mu opioid receptor antagonist, naltrexone HCl has no sympathomimetic effects, and clinical experience has not revealed consistent effects on vital signs (86–88). Hence, naltrexone HCl is unlikely to be responsible for blood pressure and heart rate effects observed after NB administration. <u>Bupropion HCl historical experience</u> 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 (84). Its observed haemodynamic profile has been well established and is described in the bupropion HCl product information (77). <u>Naltrexone HCl historical experience</u> As a mu opioid receptor antagonist, naltrexone HCl has no sympathomimetic effects, hence is unlikely to be responsible for any blood pressure or heart rate effect.

Important Identified Risk –INCREASES IN BLOOD PRESSURE OR HEART RATE	
Evidence source(s) and strength of evidence	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. In the integrated summary of the clinical trials supporting the registration of NB, minimal changes in mean resting pulse rate were observed for subjects in all groups over time. An analysis using pre-specified criteria for pulse showed a higher incidence of pulse increases in the Total NB group compared with the Placebo group. An analysis for pulse showed a higher incidence of pulse increases in the NB group compared with the Placebo group. In subgroup analyses evaluating prespecified criteria for pulse, neither race, ethnicity, baseline antihypertensive medication use, nor baseline obesity class had a consistent effect. A generally higher incidence of subjects experiencing increases in pulse was apparent in males and younger subjects in both the NB and Placebo groups. Subjects receiving NB and having a $\geqslant$5% weight loss at endpoint also showed increased incidence in the prespecified criteria for pulse, the opposite pattern was observed in the Placebo group. Overall in the NB clinical trials, a placebo corrected mean increase from baseline in systolic and diastolic blood pressure of up to 1 mm Hg was observed. Mean systolic and diastolic blood pressure showed initial increases of approximately 1 mm Hg in the NB group at Weeks 4 and 8. After this, both mean systolic and diastolic blood pressure began to decrease at each timepoint to Week 28 (systolic) and Week 24 (diastolic) after which, changes in blood pressure from baseline were maintained at approximately 1 mm Hg below baseline values (for each). In the Placebo group, mean systolic blood pressure decreased from baseline over time at each endpoint reaching an average of -2.2 mm Hg below baseline. In a subgroup analysis evaluating prespecified criteria for systolic blood pressure, neither obesity class nor having a $\geqslant$5% weight loss at endpoint had a consistent effect in NB-treated subjects. Small increases in the incidence of subjects experiencing increases in the prespecified criteria for systolic blood pressure were apparent in males, non-Hispanics and subjects using antihypertensive medication in both the Total NB and Placebo groups. Blacks/African Americans showed somewhat higher incidences of prespecified systolic blood pressure criteria compared to other races, and systolic blood pressure showed a trend of increasing with age in NB-treated subjects; no consistent trend was observed for either race or age in the Placebo group. Non-smoking subjects receiving NB also showed slightly higher incidences in the prespecified criteria for systolic blood pressure, the opposite pattern was observed in the Placebo group. Overall, a greater percentage of subjects experienced Blood Pressure and Pulse TEAEs in the NB group compared with the Placebo group (5.9% and 4.2%, respectively). The majority of the events were reported within the Hypertension subtopic (5.3% NB and 4.0% Placebo); all other subtopics (Hypotension, Bradycardia, and Tachycardia) had a similar incidence of events in the Total NB and Placebo groups. No Blood Pressure or Pulse-related SAEs were reported in either the Primary or Overall datasets.

Important Identified Risk –INCREASES IN BLOOD PRESSURE OR HEART RATE	
Frequency with 95 % CI	<u>Blood pressure-related adverse events</u> Over the course of the NB double-blind clinical trials, the *incidence risk* of a hypertension Standard MedDRA Queries (SMQ)-related adverse event among all subjects treated with NB was 5.2% (n=170/3,239). In the placebo group, the incidence risk was 4.0% (n=60/1,515). The attributable risk can be calculated as 5.2%-4.0% = 1.20%. The calculated exposure-adjusted relative risk is 1.44 (95%CI: 1.08, 1.94). In NB-CVOT, AELDSM for hypertension were reported in 0.2% placebo, 0.4% NB patients and SAEs representing hypertension comprised 2 SAEs of blood pressure increased (both NB). <u>Heart rate-related adverse events</u> Over the course of the NB double-blind clinical trials, the *incidence risk* of an arrhythmia SMQ-related adverse event in NB treated subjects was 5.5% (n=179/3,239). In the placebo group, the incidence risk was 4.2% (n=63/1515). The attributable risk can be calculated as 5.5%-4.2% = 1.3%. The calculated exposure-adjusted relative risk is 1.41 (95%CI: 1.06, 1.88). In the arrhythmia SMQ, events of palpitations occurred with the greatest treatment difference (2.4% vs. 0.9%). The Tachyarrhythmia SMQ was also analysed to further understand the effects of NB when palpitations were not a component of the SMQ. Events in the Tachyarrhythmia SMQ occurred less frequently in the NB group compared with placebo (0.3% vs. 0.5%). The calculated exposure-adjusted relative risk is 0.68 (95%CI: 0.25, 1.87). In NB-CVOT AELDSM for palpitations were reported in 0.1% placebo, 0.4% NB, with AELDSM for atrial fibrillation were reported in 0.1% in both the placebo and NB groups (see CSR table 39). Overall, individual SAE preferred terms associated with heart rate-related treatment-emergent SAEs (see CSR table 37) assessed to be study-drug related includes atrial fibrillation (1 report in each treatment group), palpitations (1 report in the placebo group; 0 NB), supraventricular tachycardia (1 report in the NB group; 0 placebo), and syncope (1 report in the placebo group; 0 NB).
Severity and reversibility	Overall in the NB clinical trials, a placebo corrected mean increase from baseline in systolic and diastolic blood pressure of up to 1 mm Hg was observed. In the NB group, mean SBP and DBP showed initial increases of approximately 1 mm Hg at Weeks 4 and 8. Mean blood pressure decreased below baseline values after Week 12 and remained below baseline through Week 56. After 28 weeks of treatment, average changes in blood pressure from baseline for NB-treated subjects were maintained at approximately 1 mm Hg below baseline values. In the placebo group, mean SBP decreased from baseline over time at each time point to Week 24, reaching 2 mm Hg below baseline; mean DBP in the placebo group showed a consistent decrease across monthly time points of approximately 2 mm Hg below baseline. Initial increases in SBP and DBP are consistent with the mild sympathomimetic effects of bupropion HCl (84,85). The gradual decreases in mean blood pressure observed after Week 8 follow the time course of weight loss in the study population and are consistent with the weight loss-related attenuation of the bupropion HCl pressor effect. For most subjects in both treatment groups increases in vital sign values were sporadic, transient, and resolved without anti-hypertensive medication with continued study drug treatment. As a result of the relative increase in blood pressure (~1 - 2 mmHg) and in heart rate (~1.5 bpm) observed with NB compared to placebo in Phase 3 clinical studies, the FDA requested a large cardiovascular outcomes trial (NB-CVOT study) to evaluate whether the increase in blood pressure and pulse translates to an increase in cardiovascular event rates. The NB-CVOT study was designed to evaluate the impact of NB therapy on major adverse cardiovascular events in obese subjects with increased cardiovascular risk. The final results from the analysis of this study did not suggest an increased risk for major cardiovascular events.

Important Identified Risk –INCREASES IN BLOOD PRESSURE OR HEART RATE	
	An additional CVOT study is ongoing (NB-CVOT-3, INFORMUS) to evaluate the cardiovascular safety of study subjects receiving NB.
Seriousness/long term outcomes	In the NB double-blind clinical trials, discontinuations due to a hypertension SMQ-related event were rare both in NB treated subjects (n=23/3239, 0.7%) as well as in those treated with placebo (n=3/1515, 0.02%). Discontinuations due to an arrhythmia SMQ-related event were rare both in NB treated subjects (n=20/3,239, 0.6%) as well as in those treated with placebo (n=8/1,515, 0.05%). Palpitations infrequently led to discontinuations (0.3% for NB; none for placebo). Discontinuations due a tachyarrhythmia SMQ-related event were rare and less frequent in the NB group compared with placebo (<0.1% vs. 0.2%).
Impact on quality of life	A review of the literature found no studies that evaluated the effect of hypertension on health-related quality of life in obese adults.
Background incidence/ prevalence	In the Framingham Heart Study (134), a 5% weight gain was associated with a 20–30% increase in hypertension incidence, and the Harvard Male Alumni (135) study found a weight gain of 25 pounds was associated with a 60% increase in hypertension incidence. Weight gain is associated with increases in arterial pressure, and it has been estimated that 60–70% of hypertension in adults is attributable to adiposity. Obesity-related hypertension may be a distinct hypertensive phenotype with distinct genetic determinants. Mechanisms of obesity-related hypertension include insulin resistance, sodium retention, increased sympathetic nervous system activity, activation of renin–angiotensin–aldosterone, and altered vascular function (136).
Risk groups or risk factors	Risk groups or risk factors associated with increases in blood pressure following NB therapy include patients with history of high blood pressure and patients with uncontrolled hypertension.
Preventability	The risk of increases in blood pressure associated with NB exposure can be reduced through routine and additional risk minimisation activities. The SmPC for NB lists *uncontrolled hypertension* as a contraindication and provides a detailed discussion on issues related to hypertension in (Section 4.4 Special warnings and precautions for use: the SmPC specifies that 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. Treatment with Mysimba should thus be discontinued if there are concerns with the safety or tolerability of ongoing treatment, including concerns about increased blood pressure. Additionally, SmPC Section 4.2 Posology and method of administration specifies that annual assessment should be conducted by the healthcare professional in discussion with the patient when considering treatment continuation to ensure maintenance of a loss of at least 5% of their initial body weight and no adverse change in patient cardiovascular risk. Further, Section 4.4 Special warnings and precautions for use specifies that physicians prescribing NB must have received and must be familiar with the physician educational material, and must discuss benefits and risks of NB therapy with the patient.
Impact on the risk-benefit balance of the product	Obese patients have a higher risk of heart disease and stroke, which might lead to death. Weight loss is generally associated with decreases in mean blood pressure; while this effect was observed for both NB and placebo subjects it was greater for placebo. Endpoint values for blood pressure were either unchanged or decreased relative to baseline with NB treatment. In addition, NB subjects who lost at least 5% of their initial body weight had reductions from baseline in mean blood pressure. Mysimba is a prescription medicine used along with diet and exercise to treat obesity. NB should be used with caution in patients with hypertension, a history of cardiovascular disease and when

Important Identified Risk –INCREASES IN BLOOD PRESSURE OR HEART RATE	
	administered concomitantly with agents that are known to increase blood pressure. The risk of increases in blood pressure associated with NB exposure can be reduced through routine and additional risk minimisation activities. The SmPC for NB lists uncontrolled hypertension as a contraindication and provides a detailed discussion on issues related to hypertension (NB Section 4.4 Special Warnings and Precautions for Use). Additionally, the SmPC specifies the blood pressure and pulse should be measured prior to initiation of therapy with NB 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 NB treatment, it should be discontinued. Treatment with Mysimba should be discontinued if there are concerns with the safety or tolerability of ongoing treatment, including concerns about increased blood pressure (NB SmPC Section 4.4). Additionally, SmPC Section 4.2 Posology and method of administration specifies that annual assessment should be conducted when considering treatment continuation to ensure maintenance of a loss of at least 5% of their initial body weight and no adverse change in patient cardiovascular risk. Further, Section 4.4 Special warnings and precautions for use specifies that physicians prescribing NB must have received and must be familiar with the physician educational material, and must discuss benefits and risks of Mysimba with the patient. Overall, recommendations and precautions to be followed by healthcare professionals and patients for the safe and effective use of Mysimba have been included in the summary of product characteristics and the package leaflet. In addition to routine risk minimisation measures, this risk associated with NB exposure can be reduced through additional risk minimisation activities and is thus already highlighted in the Physician Prescribing Checklist (PPC) that has been implemented as a risk minimisation tool. Increases in blood pressure or heart rate will continue to be monitored as part of the routine PV plan for NB. An additional CVOT study (NB-CVOT-3, INFORMUS) to evaluate the cardiovascular safety of study subjects receiving NB is ongoing. The benefit-risk profile for Mysimba® remains favourable.
Public health impact	The potential public health impact of increases in blood pressure or heart rate is expected to be minimal given that the majority of the blood pressure-related adverse events were considered to be mild. A review of the literature on changes in blood pressure in the adult obese population who may have been exposed to bupropion HCl or naltrexone HCl did not result in any findings. The NNH can be calculated as 1/AR = 1/0.012 = 83; therefore, approximately 83 obese adults would need to be treated with NB before observing 1 treatment-emergent case of rise in blood pressure assuming a casual association between NB use and elevation in blood pressure. In addition to data hitherto available, the CVOT study (NB-CVOT-3, INFORMUS), to evaluate the cardiovascular safety of study subjects receiving NB, is ongoing.
Reference source	(77) Zyban SmPC 2018 (84) Settle EC et al. 1999 (85) Thase ME et al. 2008 (86) Thomas M et al. 1976 (87) Crabtree BL. et al. 1984 (88) Ring C et al. 2008

Important Identified Risk – HYPERSENSITIVITY REACTIONS, INCLUDING SEVERE CUTANEOUS ADVERSE REACTIONS [STEVENS-JOHNSON SYNDROME (SJS), ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS (AGEP)]	
MedDRA terms	SMQ: Hypersensitivity
Potential mechanisms	The potential mechanisms behind the putative effect of NB on hypersensitivity are unknown.

Important Identified Risk – HYPERSENSITIVITY REACTIONS, INCLUDING SEVERE CUTANEOUS ADVERSE REACTIONS [STEVENS-JOHNSON SYNDROME (SJS), ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS (AGEP)]	
Evidence source(s) and strength of evidence	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. In the integrated summary of the clinical trials supporting the registration of NB, the incidence of Hypersensitivity Reaction/Skin Rash events was similar in the NB group compared with the Placebo group (13.4% and 15.2%, respectively) in the Primary Dataset and there was no difference in the incidence of SAEs ($\leqslant$0.1% in both groups), and the percentage of subjects who discontinued due to these events was also similar (NB 1.9% and Placebo 1.2%). Among the subjects who reported Hypersensitivity Reaction/Skin Rash events as a TEAE, initial onset was observed within the first 8 weeks in approximately half of subjects in the NB group and approximately one third of subjects in the Placebo group. The median time to onset for Hypersensitivity Reaction/Skin Rash events was shorter in the NB group compared to Placebo (7 vs. 15 weeks, respectively). The median duration of Hypersensitivity Reaction/Skin Rash events was 2 weeks in both the Total NB group and the Placebo group. There was no difference in the cumulative probability of reporting Hypersensitivity Reaction/Skin Rash between the Total NB and Placebo groups. In relation to AGEP in particular, for the mono-component bupropion, the product information was updated for the mono-component buproprion to include AGEP as a reaction (4.8), with warning & precaution text in SmPC 4.4. For NB, a low number of probably or possibly related cases have been reported.
Frequency with 95 % CI	In the NB clinical trials programme, the *incidence risk* of hypersensitivity among subjects treated with NB was 13.4% (95%CI 12.2%-14.6%; n=434/3239). In the placebo group, the incidence risk was found to be 15.2% (95%CI 13.5%-17.2%; n=231/1515). The attributable risk for treatment-emergent adverse event for hypersensitivity can be calculated as 13.4% - 15.2% = -1.8% (95%CI: -4.0%, 0.31%). The relative risk can be calculated as 0.13/0.15 = 0.88 (95%CI: 0.76, 1.02). Severe cutaneous adverse reactions such as SJS and AGEP have been rarely reported.
Severity and reversibility	Of all events in the NB-treated group, 67% were mild; 30% were moderate; and 3% were severe in severity. Of all events in the placebo group, 69% were mild; 28% were moderate; and 3% were severe. Of those who experienced a hypersensitivity-related adverse event in the NB group (n=3239), 271 experienced a systemic reaction (8.4%), 187 experienced a skin reaction (5.8%), and 15 experienced a local reaction (0.5%). In the placebo group, 161 had a systemic reaction (10.6%), 81 experienced a skin reaction (5.3%) and 9 experienced a local reaction (0.6%). A total of 5 serious cases of hypersensitivity were reported in the NB clinical development programme. Only 3 (0.7%) of the 434 cases of hypersensitivity-related adverse events in the NB group were considered to be serious, all of which occurred as a systemic reaction. In the placebo group, 2 (0.9%) cases of hypersensitivity-related adverse events were considered to be serious, both of which were also due to a systemic reaction. Angioedema, oedema/swelling of the lips, mouth and pharynx, and throat tightness were reported in those who experienced a systemic reaction among NB-treated subjects in the NB clinical trials programme, while anaphylactic reaction and swelling of face and tongue were reported in the

Important Identified Risk – HYPERSENSITIVITY REACTIONS, INCLUDING SEVERE CUTANEOUS ADVERSE REACTIONS [STEVENS-JOHNSON SYNDROME (SJS), ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS (AGEP)]	
	placebo group. Potential allergic symptoms, the most common of which were oropharyngeal pain and cough were frequent but not specific for allergy. Rash were generally mild in the skin reactions. There were no rashes suggestive of erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, or acute generalised exanthematous pustulosis in the NB clinical trials programme. Bupropion historical experience Symptoms of hypersensitivity associated with bupropion exposure include skin rash, pruritus, urticaria or chest pain but more severe reactions may include angioedema, dyspnoea/bronchospasm, anaphylactic shock, erythema multiforme or Stevens-Johnson Syndrome (77). Arthralgia, myalgia and fever have also been reported in association with rash and other symptoms suggestive of delayed hypersensitivity.
Seriousness/long term outcomes	In the NB-treated group, out of 434 events 0.7% were serious and in the placebo group, 0.9% of incidences were serious. Among the 3239 subjects treated with NB, 60 subjects (1.9%) *discontinued* treatment resulting from a hypersensitivity treatment-related adverse event. Among the 1515 placebo treated patients, 18 (1.2%) discontinued therapy.
Impact on quality of life	A review of the literature found no studies on the potential effect of hypersensitivity on HRQOL in the adult obese population.
Background incidence/prevalence	Background incidence or prevalence of hypersensitivity in the untreated adult obese population could not be identified based on a review of the literature.
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.
Preventability	In the *bupropion* experience, most patients' symptoms improved after stopping bupropion and initiating treatment with antihistamine or corticosteroids, and resolved over time (77). The risk of hypersensitivity associated with NB exposure can be reduced through routine risk minimisation activities. The SmPC for NB lists hypersensitivity to naltrexone, bupropion or NB excipients as a contraindication (NB SmPC Section 4.3). The SmPC also includes language about allergic reactions (including Stevens-Johnson syndrome and acute generalized exanthematous pustulosis) in Section 4.4 Special Warnings and Precautions for Use, advising to monitor closely, withdraw immediately if signs and symptoms appear and to not restart in the patient at any time in case of a serious reaction such as SJS or AGEP.
Impact on the risk-benefit balance of the product	To date, there were no signals involving hypersensitivity related reports in the Global safety database. The occurrences analysed in the postmarketing surveillance to date are consistent with the known pharmacologic profiles of the individual components as well as the guidance to the prescriber presented in the Mysimba SmPC and other worldwide product labelling. The risk of hypersensitivity associated with NB exposure can be reduced through routine risk minimisation activities. Mysimba should not be used in patients who are allergic to NB or to any of the other ingredients of the medicine (NB SmPC section 4.3). If an allergic reaction is suspected, treatment with Mysimba should be stopped and not restarted. The SmPC also includes language about allergic reactions (including the severe cutaneous adverse reactions Stevens-Johnson syndrome and acute generalized exanthematous pustulosis) in Special Warnings and Precautions for Use (NB SmPC section 4.4). This risk will continue to be monitored as part of the routine PV plan for NB. The benefit-risk profile for Mysimba remains positive
Public health impact	The public health impact of hypersensitivity to NB is expected to be minimal given the near absence of serious adverse events in the clinical trials programme. A review of the literature on hypersensitivity in the adult obese population who may have been exposed to bupropion or naltrexone did not

Important Identified Risk – HYPERSENSITIVITY REACTIONS, INCLUDING SEVERE CUTANEOUS ADVERSE REACTIONS [STEVENS-JOHNSON SYNDROME (SJS), ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS (AGEP)]	
	result in findings indicating an overall public health impact. The NNH could not be calculated for hypersensitivity given that the attributable risk was found to be negative.
Reference source	(77) Zyban SmPC 2018

Important Identified Risk – NEUROPSYCHIATRIC SYMPTOMS	
MedDRA terms	SMQ: Depression and suicide/self-injury
Potential mechanisms	Potential mechanisms behind the theoretical putative effect of NB on depression and mania are unknown. Some studies have suggested that manic episodes may be generally associated with an episode-dependent neuroanatomic degeneration as measured by grey matter volume and N-acetylaspartate (99) (100). Manelli *et al.* (101) suggests that GABA-glutamate imbalance is thought to play a role in the development and expression of anxiety, a common symptom in naltrexone-treated patients. Settle *et al.* reported that the association between bupropion and agitation was dose-dependent: subjects who received a 150mg, 300mg, and 400 mg daily dose experienced a 1.7%, 3.1% and 8.8% incidence of agitation, respectively (102).
Evidence source(s) and strength of evidence	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. In the integrated summary of the clinical trials supporting the registration of NB, there was a higher percentage of subjects with Psychiatric events in the NB group compared with the Placebo group in the Primary Dataset. Serious Psychiatric events were rare (reported in only one subject: anxiety) and discontinuations due to Psychiatric events were reported in a similar percentage of subjects in the NB and Placebo groups. Subjects with a prior history of depression experienced higher rates of Psychiatric events than subjects without a history of depression in both NB and Placebo groups, respectively. A history of anxiety was also associated with a higher incidence of psychiatric events in both NB and Placebo groups. Subjects $\geqslant$ 65 years of age in the NB group experienced more Psychiatric Disorders SOC events compared to Placebo although the sample size was small (62, 32) for NB and Placebo, respectively, and primarily diabetic. 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 NB and Placebo groups. The AE incidence in the Depression subtopic was similar between treatment groups and events were rarely severe. Most NB-treated subjects with Depression events had an onset during the first 8 weeks of treatment, with a similar median time to onset of 4 and 9 weeks and a similar median duration of 4 weeks and 5 weeks in the NB and Placebo groups, respectively. Discontinuations due to AEs were lower in the NB group compared to Placebo. Subjects with a history of depression had a higher

Important Identified Risk – NEUROPSYCHIATRIC SYMPTOMS	
	incidence of Depression events than subjects without a history of depression. A meta-analysis for suicidal ideation or worse (suicidality or suicidal behavior and ideation, based upon C-CASA categorization) was performed. There were no completed suicides, suicide attempts, or preparatory acts toward imminent suicidal behavior in any treatment group. There were four events of suicidal ideation or behavior during this study, one event (1/3239, <0.1%) in the NB treatment group compared to three events (3/1515, 0.2%) in the Placebo group. The overall odds ratio for suicidal ideation or worse for NB compared to Placebo was 0.14 (95% CI: 0.00, 1.72), suggesting there is no treatment difference for suicidal behavior. The overall risk difference between treatment groups (NB-Placebo) was -0.0018 (95% CI: -0.0042, 0.0007), which further supports the null hypothesis of no treatment effect on incidence of suicidal ideation or behavior.
Frequency with 95 % CI	Psychiatric special topic data in the primary NB safety dataset included subgroups of anxiety, depression, sleep disorders, and suicide/self-injury. In the NB clinical trials programme, the incidence risk of neuropsychiatric symptoms among subjects treated with NB was 16.7% (95% CI 15.4%-18.0%; n=541/3239). In the placebo group, the incidence risk was 12.9% (95%CI 11.3%-14.8%; n=196/1515). The attributable risk for treatment-emergent adverse event for neuropsychiatric symptoms can be calculated as 16.7% - 12.9% = 3.8%. The relative risk can be calculated as 0.17/0.13 = 1.3. The most common psychiatric event in the NB group was insomnia (in the Sleep Disorders subgroup). Serious psychiatric events were rare (one event of anxiety reported in an NB32-treated subject) and discontinuations due to psychiatric events were infrequent and reported in a similar percentage of subjects in the Total NB and placebo groups (2.8% and 2.6%, respectively). Patients with a serious psychiatric condition, including mania, were excluded from the NB clinical trial programme. No patients experienced a manic episode over the course of the NB clinical trials programme. In the NB clinical trials programme, the *incidence risk* of a depression-related AE with NB use was 2.8% (95%CI: 2.3%-3.4%; n=91/3239). In the placebo group, the incidence of depression was reported to be 3.4% (95%CI: 2.6%-4.5%; n=52/1515). The attributable risk of depression can be calculated as 2.8% - 3.4% = -0.6% (95%CI: -1.7%, 0.046%). The relative risk can be calculated as 0.028/0.034 = 0.82 (95%CI: 0.59, 1.14). In the NB clinical trials programme, the incidence proportion of an anxiety related AE with NB use was 6.0% (95%CI: 5.2%-6.9%; n=195/3239). Of those who experienced an anxiety-related AE, 127 subjects (3.9%, 95%CI: 3.3%-4.6%) experienced anxiety, 74 subjects (2.3%, 95%CI: 1.8%-2.9%) experienced irritability, and 8 subjects (0.25%, 95%CI: 0.11%-0.49%) experienced agitation. The incidence proportion of an anxiety related AE among unexposed (placebo) subjects was 4.4% (95%CI: 3.4%-5.6%; n=67/1515). Of those who experienced an anxiety-related AE, 43 subjects (2.8%, 95%CI: 2.1%-3.8%) experienced anxiety, 28 subjects (1.8%, 95%CI: 1.2%-2.7%) experienced irritability, and 1 subject (0.07%, 95%CI: 0.002%-0.37%) experienced agitation. The attributable risk of anxiety can be calculated as 6.0% - 4.4% = 1.6%. The relative risk can be calculated as 0.06/0.044 = 1.4. In NB-CVOT, a higher incidence of AELDSM of nervous system disorders in NB-treated subjects (1.2% placebo, 5.3% NB) was primarily due to events of tremor (0% placebo, 1.8% NB), dizziness (0.2% placebo, 1.5% NB), headache (0.3% placebo, 1.1% NB), dysgeusia (0% placebo, 0.4% NB), and disturbance in attention (<0.1% placebo, 0.2% NB). AELDSM of Psychiatric Disorders occurred more frequently in subjects receiving NB (0.9% placebo, 3.2% NB), primarily due to insomnia (0.4% placebo, 0.9% NB), anxiety (0.2% placebo, 0.6% NB), hallucination

Important Identified Risk – NEUROPSYCHIATRIC SYMPTOMS	
	(0% placebo, 0.2% NB), and nervousness (0% placebo, 0.2% NB). AELDSM of depression occurred at a relatively similar incidence between treatments (0.2% placebo, 0.1% NB). Overall, SAEs in the Nervous System Disorders SOC were similar between the treatment groups (0.6% placebo, 0.8% NB). SAEs of syncope, while infrequent, occurred at a marginally higher rate in the NB treatment group (5 events: 0.1% placebo; 7 events: 0.2% NB). All cases of syncope were subject to adjudication for potential MACE; all were adjudicated non-MACE. In the Psychiatric Disorders SOC, SAEs occurred at a low incidence (<0.1% placebo, 0.2% NB). Neuropsychiatric serious adverse events in subjects receiving NB assessed to be related to study medication (CSR table 37) included one SAE of hallucination in a patient receiving NB and 1 SAE of suicidal ideation in a patient receiving placebo.
Severity and reversibility	No patients experienced a manic episode over the course of the NB clinical trials programme. Depression was of special interest in the NB development programme because of historical concerns surrounding both obesity and antidepressant treatment in relation to suicidality. There were no cases of *serious* adverse events attributable to depression in the NB clinical trial programme. Of all (n=91) events in the NB-treated group, 46% were mild; 47% were moderate; and 8% were severe. Of all (n=52) incidences in the placebo group, 46% were mild; 50% were moderate; and 4% were severe in severity. An association between depression and obesity has been well-established in clinical studies (89) and an epidemiological study (90). Risk of depression was assessed in multiple ways throughout the NB clinical program, including AEs, Columbia Classification Algorithm of Suicide Assessment (C-CASA), IDS-SR, and a small open-label study in obese/overweight and depressed subjects (NB-402, N=25). A thorough review of this data revealed no increased risk of depression or suicidality with NB treatment. Of those who experienced an anxiety related adverse event, only 1 case (0.03%, 95%CI: 0.0008%-0.17%; n=1/3239) was considered to be serious. The case of anxiety was reported in the NB32 group in a [redacted]-year-old [redacted] female with an active history of asthma. The subject was hospitalised with anxiety accompanied by dyspnea on exertion, angina pectoris and palpitations and discontinued study drug due to the primary event of dyspnea exertional. It is possible that the anxiety event was related to the initial dyspnea.
Seriousness/long term outcomes	No patients experienced a manic episode over the course of the NB clinical trials programme. None of the events of depression was considered serious or resulted in fatality. Among the 3239 subjects treated with NB, 30 subjects (0.9%) discontinued treatment resulting from a depression-related adverse event. In the placebo treated group (n=1515), 18 subjects (1.2%) discontinued therapy resulting from a depression-related adverse event. Among the 3239 subjects treated with NB, 21 subjects (0.65%, 95%CI: 0.40%-0.98%) discontinued treatment resulting from an anxiety related adverse event. In the placebo treated group (n=1515), 10 subjects (0.66%, 95% CI: 0.25-1.07%) discontinued therapy resulting from an anxiety related adverse event.
Impact on quality of life	A review of the literature could not identify any published source which measured the impact of mania, depression or of anxiety on HRQOL in the adult obese population.
Background incidence/prevalence	A review of the literature could not identity a background incidence or prevalence for mania in the untreated target population. The Third National Health and Nutrition Examination Survey (1988–1994) reported that the prevalence of DIS/DSM-III major depression was 2.42% (4.01% female; 1.37% male) in overweight subjects (BMI 25.0-29.9

Important Identified Risk – NEUROPSYCHIATRIC SYMPTOMS	
	kg/m^2) and 5.12% (6.74% female; 2.85% male) in obese subjects (BMI ≥ 30 kg/m^2) (91). A prevalence rate up to 66.2% of depressive symptoms has been reported amongst a severely obese population (mean BMI of 47.0 ± 7.9 kg/m^2), which is far greater than the general population rates of 11.4% for depressive disorders in the UK (32). In the sibutramine trial of 605 obese patients, the background incidence of depression in the placebo group was reported to be 4% (5/115) over a 2 year follow-up period, or approximately 2% over a 1-year period (92). With regards to bupropion, anxiety is listed as a common adverse event in the Zyban SmPC (Section 4.8 Undesirable effects). Safety of bupropion using prescription event monitoring (PEM) 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% (93). No serious adverse events related to anxiety were reported to the French pharmacovigilance database of bupropion (94). However, anxiety was listed as a very common adverse event for naltrexone (52) (Nalorex SmPC Section 4.8 Undesirable effects) which suggests an incidence proportion of >10%.
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 (62, 32) 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) (95). 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 (96). 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 (77) (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 (97). *Petry et al* reported a 3% to 5% increased risk of depression for each unit increase in BMI (90). 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 (98). 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.

Important Identified Risk – NEUROPSYCHIATRIC SYMPTOMS	
Preventability	The risks of exacerbation of mania, depression and anxiety can be prevented through routine and/or additional risk minimisation activities. The SmPC for NB contains a discussion of Neuropsychiatric Symptoms and Activation of Mania in Section 4.4 Special warning and precautions for use: '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.' For patients with mania as a part of their diagnosis of bipolar disease, NB is contraindicated.
Impact on the risk-benefit balance of the product	The most frequent neuropsychiatric coded terms in the safety database are anxiety, depression, insomnia, nervousness, and somnolence. The available data from postmarketing spontaneous reporting surveillance do not suggest that in routine clinical practice these reactions occur more frequently than expected. There were no signals or new safety trends involving neuropsychiatric related reports with a review of occurrences reported within this specific risk revealing no factors (individually or in aggregate) that would be indicative of a previously unknown or emerging safety issue. The occurrences analysed are consistent with the known pharmacologic profiles of the individual components and the fixed combination, as well as the guidance to the prescriber presented in the SmPC and other worldwide product labeling. The risks of exacerbation of mania, depression and anxiety can be prevented through routine risk minimisation and additional risk minimisation activities. The SmPC for NB contains a discussion on Neuropsychiatric Symptoms and Activation of Mania in Section 4.4 Special warning and precautions for use: '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 NB in obese subjects, which excluded subjects receiving antidepressants. NB should be used cautiously in patients with a history of mania.' For patients with mania as a part of their diagnosis of bipolar disease, NB is contraindicated. The benefits in aggregate are expected to be greater in general clinical practice, this risk is manageable through proper patient selection, adherence to SmPC warnings and Precautions instructions, in addition the PPC will be educating prescribers on the importance of appropriate patient selection and clinical management. This risk will continue to be monitored as part of the routine PV plan for NB. Based on the cumulative experience, the benefit-risk profile for Mysimba™ is considered to be favorable
Public health impact	The public health impact of mania is expected to be minimal given the absence of events in the clinical trials programme. A review of the literature on mania in the adult obese population who may have been exposed to bupropion or naltrexone did not result in any findings. The NNH could not be calculated for mania due to the absence of data on attributable risk. The public health impact of depression on NB is expected to be minimal given the rarity of events and the absence of serious adverse events found in the clinical trials programme. A review of the literature on depression in the adult obese population following bupropion or naltrexone exposure did not result in any findings. NNH could not be calculated given that the incidence risk for depression was greater in the placebo group than in the NB treated group. The public health impact of anxiety can be estimated using number needed to harm (NNH) (83). The attributable risk of anxiety in the NB clinical trial programme can be calculated by taking the inverse of the attributable risk. Given that the AR for anxiety was 0.016 (6.0%-4.4%= 1.6% = 0.016), the NNH can be estimated to be 63 (NNH = 1/AR = 1/0.016 = 63). Therefore,

Important Identified Risk – NEUROPSYCHIATRIC SYMPTOMS	
	approximately 63 obese adults would need to be treated with NB before observing 1 treatment-emergent case of anxiety.
Reference source	Mania: (99) Frye MA et al. 2007 (95) Gao K et al. 2008 (100) Lyoo IK et al. 2004 (96) Truman CJ et al. 2007 Depression: (89) Gariepy G et al. 2010. (32) Jagielski AC et al. 2014 (92) James WP et al. 2000 (91) Onyike CU et al. 2003 (90) Petry NM et al. 2008 (98) Stunkard AJ et al. 2003 Anxiety: (93) Boshier A et al. 2003 (94) Beyens M-N et al. 2008 (52) Nalorex SmPC 2018 (101) Mannelli P et al. 2011 (102) Settle EC Jr et al. 1998 (83) Citrome L et al. 2010

Important Identified Risk – HEPATOTOXICITY	
MedDRA terms	SMQ: Hepatic disorders
Potential mechanisms	The potential mechanism behind the putative association between NB and hepatic impairment are unknown. However, the mechanism is likely to involve an intentional overdose of naltrexone as it has been shown to cause hepatocellular injury when given in high doses (daily doses >300 mg). An increase in naltrexone AUC of approximately 5- and 10-fold in patients with compensated and decompensated liver cirrhosis, respectively, compared with subjects with normal liver function has been reported. These data suggest that alterations in naltrexone bioavailability are related to liver disease severity (105). Naltrexone is extensively metabolised by the liver and excreted predominantly in the urine (52). Hepatoxicity is unlikely to occur resulting from unintentional overdose due to the high dose requirements for overdose. Hepatotoxicity was not observed in the NB phase 2/3 clinical program which utilised a maximum daily dose of naltrexone ☐ 50 mg. 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. 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. (NB SmPC Section 5.3).
Evidence source(s) and strength of evidence	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).
Frequency with 95 % CI	Of the 3239 subjects who received NB over the course of the NB clinical trials programme, 40 subjects (1.23; 95% CI: 0.85%-1.61%) experienced any form of hepatic-related adverse event (defined as ALT/AST increase, blood bilirubin increase, hepatic enzyme increase, hepatic function increase, or an abnormal liver function test). Of the 1515 subjects who received placebo, 16 subjects (1.06%; 95%CI: 0.60%-1.70%) experienced a hepatic-related adverse event. The attributable risk can be calculated as 1.23-1.06=0.17. The relative risk can be calculated as 1.23%/1.06%=1.16.

Important Identified Risk – HEPATOTOXICITY	
	In NB-CVOT, only serious adverse events and adverse events leading to the discontinuation of therapy with NB were collected. Therefore, a direct comparison of the event rates in NB-CVOT to those observed in the NB clinical trials programme is not possible. In that study within the Hepatobiliary Disorders SOC, there was one SAE assessed to be related to the use of study drug, with that event being drug-induced liver injury (DILI) in a patient receiving NB. Overall, within the Hepatobiliary Disorders SOC, an equal incidence of reported SAEs was noted between treatment groups (0.6% each) (see CSR table 38).
Severity and reversibility	Hepatotoxicity was not observed in the NB phase 2/3 clinical program which utilised maximum daily doses of naltrexone ≤50 mg and maximum daily doses of bupropion up to 400 mg, both in a prolonged release formulation (at the exception of one Phase 2 study which used naltrexone 50 mg IR). The lack of observed hepatotoxicity with NB was expected since naltrexone doses selected for the NB combination (daily doses 50 mg or less) were well-below those associated with hepatotoxicity (daily doses >300 mg). Events related to elevation in alkaline phosphatase or bilirubin were rare in the NB clinical development programme (<0.1% in both treatment groups) and none were considered to be serious. No subjects met Hy's Law criteria. Analysis of clinical chemistry parameters related to liver function (ALT, AST, albumin, and bilirubin) also showed no apparent differences between patients treated with NB or placebo. There were no meaningful differences in the incidence of hepatotoxicity between the NB and placebo groups with respect to age, race, BMI class, transaminase > 3 X ULN during study, weight loss ≥5%, alcohol use, or diabetes history. The possible occurrence of hepatic impairment following NB use could possibly be attributed to an overdose of naltrexone (i.e., daily doses >300 mg). The post-marketing experience for naltrexone has shown that it can lead to liver disorder, increases in bilirubin, hepatitis, transient increase in liver transaminases, and occasional liver function abnormalities (52). In light of naltrexone's successful clinical use as an opioid antagonist over 40 years, some researchers have suggested that naltrexone has no potential for significant hepatotoxicity (103). Hepatic impairment has not been demonstrated to be a safety concern for bupropion during its 30-year post-marketing experience.
Seriousness/ long term outcomes	Only 0.25% (8/3239) and 0.13% (2/1515) patients in the NB and placebo groups, respectively, discontinued treatment due to a hepatic-related AE. In NB-CVOT, only serious adverse events and adverse events leading to the discontinuation of therapy with NB were collected. In NB-CVOT in the Hepatobiliary Disorders SOC, there was a single SAE assessed to be related to the use of study drug, with that event being drug-induced liver injury (DILI) in a patient receiving NB. The subject recovered with hepatic enzyme levels within the normal range. The causality assessment was confounded by the use of other concomitant medications with potential to contribute to drug-induced liver injury at the time of the event; however, given the temporal association and the resolution of the event after study medication discontinuation, causal relationship to NB could not be excluded. Overall, within the Hepatobiliary Disorders SOC, with respect to treatment-emergent findings, an equal incidence of reported SAEs was noted between treatment groups (0.6% each) (see CSR table 38). In addition, in NB-CVOT treatment-emergent hepatic-related adverse event (defined as ALT/AST increase, blood bilirubin increase, hepatic enzyme increase, hepatic function increase, or an abnormal liver function test) resulting in the discontinuation of therapy were reported at a very low rate

Important Identified Risk – HEPATOTOXICITY	
	(4 events). This included 2 events of ALT increased (both in a subject receiving placebo), 1 event of AST increased (also in a subject receiving placebo), and 1 event of hepatic enzyme increased (a subject receiving NB) (see CSR table 15.2.1-4.1B).
Impact on quality of life	A review of the literature could not locate any published source which measured the impact of hepatic impairment on HRQOL in the adult obese population.
Background incidence/ prevalence	Background incidence and prevalence of hepatic impairment in the untreated adult obese population could not be located following a review of the published literature. Data from a US based population health survey (NHANES III [2011-2012](104)) demonstrate the proportion of obese individuals with even mild increases in alanine aminotransferase (ALT; 0.26%), aspartate aminotransferase (AST; 0.7%) or bilirubin (0.15%) are exceedingly low and are similar to (ALT and AST) or lower than (bilirubin) individuals of normal or low bodyweight.
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 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 (52).
Preventability	Hepatic impairment can be prevented in NB users through routine risk minimization activities. NB is contraindicated in patients with severe hepatic impairment (SmPC Section 4.3). In this submission, it is proposed that Section 4.2 of the NB SmPC state that NB is not recommended in patients with moderate hepatic impairment and contraindicates its use in patients with severe hepatic disease; Section 4.4 provides further information.
Impact on the risk-benefit balance of the product	Hepatotoxicity is listed in the SmPC under Special warnings and precautions for use. In addition, the SmPC lists several hepatic PTs as previously observed with naltrexone, bupropion mono products and the NB combination. To date the occurrences analysed via postmarketing surveillance are consistent with the known pharmacologic profiles of the individual components and the fixed combination as well as the guidance to the prescriber presented in the SmPC, Physician Prescribing Checklist and other worldwide product labelling. There were no signals involving hepatotoxicity related reports with a review of occurrences reported within this specific risk revealing no factors (individually or in aggregate) that would be indicative of a previously unknown or emerging safety issue. Hepatotoxicity can be prevented in NB users through routine risk minimisation activities. NB is contraindicated in patients with severe hepatic impairment (SmPC Section 4.3). Section 4.2 of the NB SmPC states that NB is not recommended in patients with mild or moderate hepatic impairment and contraindicates its use in patients with severe hepatic disease, Section 4.4 provides further information. In this submission, he MAH is proposing that Section 4.2 of the NB SmPC state that NB is not recommended in patients with moderate hepatic impairment and contraindicates its use in patients with severe hepatic disease. The risk of hepatotoxicity and hepatic enzymes increased have been included in the product information. Hepatotoxicity reactions will continue to be monitored as part of the routine PV plan for NB. Based on cumulative experience, the risk Benefit profile for Mysimba remains favourable.
Public health impact	The public health impact of hepatic impairment is expected to be minimal given the rarity of events on hepatic impairment and the absence of severe adverse events found in the clinical trials programme. A review of the literature on hepatic impairment in the adult obese population who may have been exposed to bupropion or naltrexone did not result in any findings. The NNH can be calculated as 1/AR = /0.0017 = 588; therefore, approximately 588 obese adults would need to be treated with NB before

Important Identified Risk – HEPATOTOXICITY	
	observing 1 treatment-emergent case of hepatic-related adverse event assuming that a causal association exists between hepatic-related adverse event and NB use.
Reference source	(52) Nalorex SmPC 2018 (103) Brewer C et al. 2010. (105) Naltrexone US PI. 2013

Important Identified Risk –USE IN PATIENTS WITH HEPATIC IMPAIRMENT	
MedDRA terms	SMQ: Medical History: SMQ Level 1 - Hepatic disorders, Narrow
Potential mechanisms	Bupropion is metabolised to its major active metabolite hydroxybupropion primarily by hepatic cytochrome P450 CYP2B6; thus, the potential exists for interaction when administered with medications 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 medications metabolised by CYP2D6. Patients with hepatic impairment may have altered function of these cytochrome systems.
Evidence source(s) and strength of evidence	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. Post-approval, NB was evaluated in a single-does pharmacokinetic study in patients with varying levels of hepatic impairment where it was demonstrated that patients with severe or moderate hepatic impairment may have higher drug concentrations which may result in an increase in adverse drug reactions.
Frequency with 95 % CI	As presented in PBRER #6, the safety database was searched for any patient who experienced an AE whilst undergoing treatment with NB, who also had a medical history of hepatic impairment captured under the "Other relevant history" section of the safety database. As of the DLP for that report, there were 173 coded terms associated with the use of NB that met this definition.
Severity and reversibility	As presented in PBRER #6, in total, there were 173 reports of over a 4-year period. However, when comparing the rate of serious adverse events/reactions all time, there have been 17 coded terms contained within 7 cases. No safety concerns were identified in an evaluation of those cases.
Seriousness/ long term outcomes	In the post-approval setting, NB was evaluated in 37 patients with normal hepatic function as well as with hepatic impairment classified as mild, moderate, or severe hepatic impairment as defined by the Child-Pugh classification system, A (mild), B (moderate), or C (severe). It was concluded that patients with severe or moderate hepatic impairment may have higher drug concentrations which may result in an increase in adverse drug reactions.
Impact on quality of life	To date the reports received in patients analysed via postmarketing surveillance are consistent with the known pharmacologic profiles of the individual components and the fixed combination as well as the guidance to the prescriber presented in the SmPC, Physician Prescribing Checklist and other worldwide product labelling. There were no signals involving hepatotoxicity related reports with a review of occurrences reported within this specific risk revealing no factors (individually or in aggregate) that would be indicative of a previously unknown or emerging safety issue.
Background incidence/ prevalence	Background incidence and prevalence of hepatic impairment in the untreated adult obese population could not be located following a review of the published literature. Data from a US based population health survey

Important Identified Risk –USE IN PATIENTS WITH HEPATIC IMPAIRMENT	
	(NHANES III [2011-2012](104)) demonstrate the proportion of obese individuals with even mild increases in alanine aminotransferase (ALT; 0.26%), aspartate aminotransferase (AST; 0.7%) or bilirubin (0.15%) are exceedingly low and are similar to (ALT and AST) or lower than (bilirubin) individuals of normal or low bodyweight.
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.
Preventability	NB is subject to medical prescription. Use in patients with hepatic impairment can be prevented in NB users through routine risk minimization activities. The SmPC for NB being proposed in this submission states that NB is contraindicated in severe hepatic impairment (SmPC Section 4.3) and is not recommended in patients with moderate hepatic impairment (SmPC Section 4.2). In patients with mild hepatic impairment, the maximum recommended daily dose for NB is two tablets (one tablet in the morning and one tablet in the evening). Section 4.4 provides further information
Impact on the risk-benefit balance of the product	In the post-approval setting, NB was evaluated in 37 patients in a Phase 1, open label, parallel group, single dose study (NaltrexBuprop1005). The study included patients with normal hepatic function as well as with hepatic impairment classified as mild, moderate, or severe hepatic impairment as defined by the Child-Pugh classification system, A (mild), B (moderate), or C (severe). It was concluded that 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). 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. It was also concluded that patients with severe or moderate hepatic impairment may have higher drug concentrations which may result in an increase in adverse drug reactions. To date the occurrences analysed via postmarketing surveillance are consistent with the known pharmacologic profiles of the individual components and the fixed combination as well as the guidance to the prescriber presented in the SmPC, Physician Prescribing Checklist and other worldwide product labelling. Based on cumulative experience, the risk Benefit profile for Mysimba remains favourable.
Public health impact	The public health impact of hepatic impairment is expected to be minimal given the rarity of events on hepatic impairment and the absence of severe adverse events found in the clinical trials programme. A review of the literature on hepatic impairment in the adult obese population who may have been exposed to bupropion or naltrexone did not result in any findings. The NNH can be calculated as 1/AR = /0.0017 = 588; therefore, approximately 588 obese adults would need to be treated with NB before observing 1 treatment-emergent case of hepatic-related adverse event assuming that a causal association exists between hepatic-related adverse event and NB use.
Reference source	NB-1005; cumulative analyses of postmarketing data presented in PBRER #6

Important Identified Risk –USE IN PATIENTS WITH SEVERE OR MODERATE RENAL IMPAIRMENT	
MedDRA terms	SMQ: Medical History: SMQ Level 1 - Acute renal failure, Narrow
Potential mechanisms	Naltrexone and bupropion metabolic products are excreted in the urine. 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. 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. 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. A single-dose pharmacokinetic study has been conducted for NB 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.
Evidence source(s) and strength of evidence	The identified potential effects of renal impairment come from data obtained in a single dose pharmacokinetic study of NB, along with available literature and approved product information on bupropion HCl and naltrexone HCl.
Frequency with 95 % CI	The cumulative safety database was searched for the analysis in PBRER #6 for any patient who experienced an AE whilst undergoing treatment with NB who also had a medical history of renal impairment captured under the "Other relevant history" section of the safety database. As of the DLP for that report, there have been 42 coded terms contained within 9 cases associated with the use of NB in a patient with a history of renal impairment recorded in the safety database.
Severity and reversibility	A single-dose pharmacokinetic study evaluated patients with varying degrees of renal function (normal renal function or mild, moderate, or severe renal impairment). Based on the primary statistical analyses using CrCl-BSA criteria, increasing severity of renal impairment was associated with a statistically significant increase in the overall systemic exposure (AUCt and AUC∞) and prolongation of the t1/2z for 6β-naltrexol. In contrast, increasing renal impairment had no statistically significant effect on the pharmacokinetic parameters of naltrexone. Increasing severity of renal impairment was associated with a statistically significant increase in the overall systemic exposure (AUCt and AUC∞) to threohydrobupropion and erythrohydrobupropion, and a prolongation of the t1/2z for erythrohydrobupropion. In contrast, increasing renal impairment had no statistically significant effect on the pharmacokinetic parameters of bupropion and hydroxybupropion. 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.
Seriousness/ long term outcomes	In a single dose PK study, there were no medically relevant safety findings in subjects with varying degrees of renal function. All TEAEs resolved by the end of the study and no new TEAEs were reported beyond the known safety profile of NB.
Impact on quality of life	Overall, there were no signals involving reports received in patients with a renal history, with a review of occurrences reported within this specific patient population revealing no factors (individually or in aggregate) that would be indicative of a previously unknown or emerging safety issue. Based upon a comparison of the most frequently reported coded terms in

Important Identified Risk –USE IN PATIENTS WITH SEVERE OR MODERATE RENAL IMPAIRMENT	
	this subpopulation to the overall population of patients using NB, there does not appear to be a difference in the safety profile in patients with a history of renal impairment.
Background incidence/ prevalence	A substantial proportion of subjects in Study NB-CVOT (26.9%; n=2,394, placebo n=1,174; NB n=1220) exhibited mild or moderate renal impairment (eGFR 30 to 90 mL/min) at screening; 3.9% of these subjects were classified as having moderate renal impairment (n=348; eGFR 30-59 mL/min). Based on the data in these 2,394 patients, the safety profile of patients with mild renal failure has been characterized and is shown to be similar to that for patients without renal impairment.
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.
Preventability	NB is subject to medical prescription. NB is contraindicated patients with end-stage renal failure (NB SmPC Section 4.3). In patients with moderate or severe renal impairment, the maximum recommended daily dose for NB is two tablets (one tablet in the morning and one tablet in the evening). 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 (NB SmPC Section 4.2). Section 4.4 provides further information.
Impact on the risk-benefit balance of the product	NB was evaluated in a Phase 1, open label, parallel group, single dose study in 37 patients. The study evaluated patients with varying degrees of renal function (normal renal function or mild, moderate, or severe renal impairment). 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 (NB SmPC Section 4.2). Naltrexone / bupropion is contraindicated in end-stage renal failure (NB SmPC Section 4.3). To date the occurrences analysed via postmarketing surveillance are consistent with the known pharmacologic profiles of the individual components and the fixed combination as well as the guidance to the prescriber presented in the SmPC, Physician Prescribing Checklist and other worldwide product labelling. Based on cumulative experience, the risk Benefit profile for Mysimba remains favourable.
Public health impact	The public health impact of renal impairment is expected to be minimal given the rarity of events and the absence of severe adverse events found in the clinical trials programme. For individuals with diabetes or elderly

Important Identified Risk –USE IN PATIENTS WITH SEVERE OR MODERATE RENAL IMPAIRMENT	
	individuals, estimated glomerular filtration rate (eGFR) should be assessed prior to initiating therapy with naltrexone / bupropion in Section 4.2 Posology and method of administration and states a contraindication for endstage renal failure Section 4.3; information on renal impairment is included in Section 4.4 Special warnings and precautions for use.
Reference source	NB-1006; cumulative analyses of postmarketing data presented in PBRER #6

Important Potential Risk – SUICIDALITY IN PATIENTS WITH DEPRESSION	
MedDRA terms (PT)	Suicide/self-injury (TME) Suicide ideation, suicide attempt
Potential mechanisms	The potential mechanism behind the putative effect of NB on suicidality in the adult depressed and obese population is unknown.
Evidence source(s) and strength of evidence	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 (⩽ 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.
Frequency with 95 % CI	Over the course of the NB double-blind phase 2/3 clinical trials, the incidence risk of suicidality (defined as suicide ideation, suicide attempt, or a successful suicide evaluated clinically and with the Columbia Classification Algorithm of Suicide Assessment (C-CASA)) among subjects treated with NB was 0.03% (n=1/3239). In placebo treated subjects, the incidence risk was estimated to be 0.20% (n=3/1515). The calculated difference in incidence risk was -0.18% (95%CI: -0.42%, 0.07%). The exposure-adjusted relative risk was favourable for NB at 0.17 (95%CI: 0.02, 1.43). A single serious case of suicidality was reported in a subject treated with placebo in NB-CVOT. No SAE of treatment-emergent, study drug-related suicidality was reported in a subject with exposure to NB (see CSR table 37). While in NB-CVOT the mean duration on study drug during the Treatment Period was 53.08 weeks in the NB group and 41.72 weeks in the placebo group, subjects were continued to be followed, with the mean duration of approximately 131 weeks in both groups, and a maximum duration of 160.7 weeks (approximately 3.1 years). During this follow-up, subsequent to the treatment period, 6 events of suicidality were noted, which included 4 events in subjects that had received placebo and 2 that had received NB. These 6 events included 3 events of suicidal ideation (1 placebo and 2 NB), 1 of suicide attempt (reported in a placebo subject), and 2 completed suicides (both in placebo treated subjects) (see CSR table 41). <u>Bupropion HCl historical experience</u> Wightman *et al.* performed a meta-analysis based on FDA analysis of antidepressant suicidality data which included 8,953 adult subjects receiving bupropion HCl and 6,520 adult subjects receiving placebo from

Important Potential Risk – SUICIDALITY IN PATIENTS WITH DEPRESSION	
	randomised controlled trials with bupropion HCl conducted between 1976 and 2006 across multiple indications (106). The authors found in the major depressive disorder population, the incidence of suicidal behaviour or ideation was 17/3,179 (0.53%) versus 11/2,310 (0.48%) for the bupropion HCl and placebo groups.
Severity and reversibility	The single event of suicidality in the NB-treated group was considered to be mild in severity. Out of all (n=3) incidences in the placebo group, none were mild; 2 (67%) were moderate; and 1 (33%) was severe in severity. No subjects who received NB over the clinical trial programme experienced a serious treatment-related adverse event involving suicide ideation, suicide attempts or successful suicides. All four reported cases of suicide-related adverse events were cases involving *suicidal ideation*. Concerns over possible increased risk of suicidality with antidepressant drug use have led to heightened vigilance with respect to suicidal risk assessment for centrally-acting drugs in clinical development across a broad range of therapeutic areas. In agreement with the FDA, the C-CASA, a retrospective assessment tool of suicidality, was used to assess AEs that could represent suicidal events (behaviour and ideation). Analysis of C-CASA data was performed by an independent group blinded to treatment assignment. The results of the C-CASA analyses for the five placebo-controlled clinical trials in the Primary Dataset were pooled and analysed. Overall, there were no completed suicides, suicide attempts, or preparatory acts towards imminent suicidal behaviour in any treatment group. The data presented above for NB and placebo suggest no treatment difference for suicidal behaviour.
Seriousness/ outcomes	None of the events of suicidality was serious or fatal. Of the 3,239 subjects treated with NB, only 1 subject (0.03%) discontinued treatment as a result of suicidality. Likewise, only 1 subject (0.07%) in the placebo treated group (n=1,515) discontinued therapy.
Impact on quality of life	A review of the literature could not identify any published source which measured the impact of suicidality on HRQOL in the adult depressed and obese population.
Background incidence/ prevalence	The background incidence of suicide attempts and suicide in the obese population in Europe has been reported by Gao *et al.* who performed an epidemiological study using the UK THIN database. Incidence rate for suicide attempts in the obese population (BMI 30.0-34.9) with depression history was reported to be 228.9 per 100,000 person-years (95% CI 164.8-293.0) in men and 238.1 (95% CI 196.0-280.2) in women. Incidence rate of suicide was reported to be 1.5 (95% CI 0.8-2.3) per 100,000 person-years in obese population with a BMI > 30.0 (107).
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 (106). However, the authors found that 18- to 24-year-old group had the greatest odds of

Important Potential Risk – SUICIDALITY IN PATIENTS WITH DEPRESSION	
	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 (107).
Preventability	The risk of suicidality in patients with depression associated with NB exposure can be reduced through routine and additional risk minimisation activities. Potential risk of suicidality has been discussed extensively in Section 4.4 of the NB SmPC. Close supervision of patients and in particular young adult patients and 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.
Impact on the risk-benefit balance of the product	Obesity is known to be associated with a higher risk of depression. Obese patients have a higher risk of depression and patients with depression are more likely to be obese. Treatment with NB in the target patient population does not appear to be associated with an increased risk for depression or suicidal ideation and behaviour. Furthermore, depressed mood and suicidal tendency is a recognized symptom of the obese population. Obese patients have a higher risk of suicide as they have a higher risk of depression, which is a known risk factor for suicide. The results of the post marketing experience to date did not identify any signals involving suicidality related reports with a review of occurrences reported within this specific risk revealing no factors (individually or in aggregate) that would be indicative of a previously unknown or emerging safety issue. The occurrences analysed in the postmarketing surveillance are consistent with the known pharmacologic profiles of the individual components (specifically the anti-depressant component bupropion) and the fixed combination, as well as the guidance to the prescriber presented in the SmPC and other worldwide product labelling. Close supervision of patients, particularly those at high risk, should accompany therapy with NB 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. The risk of suicidality in patients with depression associated with NB exposure can be reduced through routine and additional risk minimisation activities and through adequate patient selection. Potential risk of suicidality has been discussed extensively in Section 4.4 Special warnings and precautions for use of the NB SmPC. In Section 4.8, Undesirable effects, suicidal ideation and suicidal behaviour are listed as having occurred with bupropion at an unknown frequency, and suicidal ideation and attempted suicide are listed as having occurred with naltrexone with a rare frequency. Mysimba is a prescription medicine and an important aspect of the PPC will be educating prescribers on the importance of appropriate patient selection and clinical management and guide physicians to prescribe Mysimba appropriately. The safety profile of NB is regularly monitored on a continuous basis by the MAH. Based on the cumulative evidence, the benefit-risk profile of Mysimba remains positive.
Public health impact	The public health impact of suicidality is expected to be minimal given the rarity of events and the absence of a clear causal association between NB use and suicidality: placebo treated subjects experienced a greater risk of suicide ideation as compared to those treated with NB. A review of the literature on suicidality in the adult obese population following naltrexone HCl or bupropion HCl exposure did not result in any findings. NNH could not be calculated given that the incidence of suicide related adverse events were higher in the placebo group than in those treated with NB.

Important Potential Risk – SUICIDALITY IN PATIENTS WITH DEPRESSION	
Reference source	(106) Wightman DS et al. 2010 (107) Gao S et al. 2013

Important Potential Risk – OFF-LABEL USE AND ABUSE POTENTIAL	
MedDRA terms (PT)	Off-label use
Potential mechanisms	Not applicable
Evidence source(s) and strength of evidence	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.
Frequency with 95 % CI	Not applicable. Subjects in the NB clinical trial programme were treated according to a specified protocol.
Severity and reversibility	Not applicable. Subjects in the NB clinical trial programme were treated according to a specified protocol.
Seriousness/long term outcomes	Not applicable. Subjects in the NB clinical trial programme were treated according to a specified protocol.
Impact on Quality of life	A review of the literature did not reveal any published source which measured the impact of off-label use on HRQOL in the adult obese population.
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 enkephalins 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 ⩽ 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).

Important Potential Risk – OFF-LABEL USE AND ABUSE POTENTIAL	
	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.
Preventability	NB is subject to medical prescription. The risk of off-label use associated with NB exposure can be reduced through routine and additional risk minimisation activities. To reduce the likelihood of off-label use, the SmPC for NB clearly indicates the therapeutic indication and the restrictions for use (NB SmPC, Section 4.1), the contraindications (NB SmPC, Section 4.3), and special warnings and precautions for use (NB SmPC, Section 4.4). In addition, physicians will be provided with a Physician Prescribing Checklist for use with each prescription of NB. This checklist emphasises the indication, contraindications and warnings. The proposed PASS program will further confirm whether NB is being prescribed in accordance with the SmPC and identify any additional guidance that may be required.
Impact on the risk-benefit balance of the product	Mysimba should only be used for weight management. Information on how well NB works in other conditions or what side effects could be seen are not available. In the postmarketing surveillance Database, there were no signals involving misuse or off-label use related reports. Overall, when reviewing reports associated with the off-label use of the NB product specifically in patients less than 18 years of age, no associated adverse events or other factors were identified which would indicate this could be potentially considered an emerging safety issue. Further, the frequency at which these occurrences are reported, and the lack of associated untoward experiences does not suggest that additional pharmacovigilance measures are necessary. NB is subject to medical prescription. The risk of off-label use associated with NB exposure can be reduced through routine and additional risk minimisation activities. To reduce the likelihood of off-label use, the SmPC for NB clearly indicates the therapeutic indication and the restrictions for use (NB SmPC, Section 4.1), the contraindications (NB SmPC, Section 4.3), and special warnings and precautions for use (NB SmPC, Section 4.4). In addition, physicians are provided with a Physician Prescribing Checklist (PPC) for use with each prescription of Mysimba. This checklist emphasises the indication, contraindications and warnings. The NB indication, dosing and administration are clearly labelled in the SmPC and it is the opinion of the MAH that this continues to be appropriate. Overall, when reviewing reports associated with the off-label use, there is no indication that the product's off-label use could be potentially considered an emerging safety issue. In the EEA, the Physician Prescribing Checklist is also a useful tool to assist with patient selection and thereby minimise off-label use or abuse. Off-label use and abuse potential will continue to be monitored as part of the routine PV plan for NB. The overall benefit-risk balance for Mysimba continues to be positive.
Public health impact	The potential public health impact of off-label use of NB is unknown given the absence of information from the clinical trials programme and the lack of relevant published findings in the literature on off-label use of bupropion HCl or naltrexone HCl in the adult obese population. The NNH could not be calculated for off-label use due to the absence of data on attributable risk.
Evidence source	(108) Crowley TJ et al. 1985

Important Potential Risk – CONGENITAL MALFORMATIONS	
MedDRA terms (PT)	Congenital birth defect; congenital cardiovascular malformation; ventricular septal defects; left outflow tract heart defect
Potential mechanisms	The potential mechanisms behind the putative association between NB and congenital malformations are unknown. Product information for the bupropion monocomponent was recently updated to state that some

Important Potential Risk – CONGENITAL MALFORMATIONS	
	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/indirect harmful effects with respect to reproductive toxicity.
Evidence source(s) and strength of evidence	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.
Frequency with 95 % CI	Of the 21 NB treated subjects who became pregnant in the clinical study programme, 11 carried to term and gave birth to a healthy infant, three had elective terminations, four subjects experienced spontaneous miscarriages, and the outcomes of three pregnancies were unknown. There were no cases of congenital malformations. Pregnancy cases in the clinical study programme of NB were too limited to draw any conclusions.
Severity and reversibility	N/A
Seriousness/ outcomes	N/A
Impact on quality of life	A review of the literature found no studies on the potential effects of congenital malformations on health-related quality of life in obese adults.
Background incidence/ prevalence	Population-based background incidence and prevalence of congenital malformations in the untreated adult obese (target) population could not be identified in our review of the literature.
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.
Preventability	The risk of congenital malformations associated with NB exposure can be reduced through routine and additional risk minimisation activities. NB should not be used in pregnancy and is subject to medical prescription.
Impact on the risk-benefit balance of the product	To date, there have been no reports of congenital malformations in the Global Safety database. The risk of congenital malformations associated with NB exposure can be reduced through routine and additional risk minimisation activities. NB is subject to medical prescription and should not be used in pregnancy or in women currently attempting to become pregnant. In addition, physicians are provided with a Physician Prescribing Checklist (PPC) for use with each prescription of Mysimba which will be educating prescribers on the importance of appropriate patient selection. The PPC states clearly if female, check whether there is any possibility of pregnancy as Mysimba must not be taken during pregnancy. Congenital anomalies will continue to be monitored as part of the routine PV plan for NB (Mysimba). The risk benefit balance of Mysimba remains favourable.
Public health impact of	The public health impact of congenital malformations is expected to be minimal given the absence of events in the clinical trials programme.
Reference source	(112) Zyban SmPC 2018

SVII.3.2. Presentation of the missing information

Safety concerns due to missing information	
Use during Pregnancy	Evidence source: Mysimba is not authorised for use in pregnancy or in women attempting to become pregnant, and it is not known if there is any risk of birth defects or whether Mysimba has any effect on growth and development in the womb. In

Safety concerns due to missing information	
	clinical studies with Mysimba, there were no cases of birth defects; however, the number of pregnancies was too small to draw conclusions. Anticipated risk/consequence of the missing information: The issue of pregnancy as potential safety issue is discussed in (NB SmPC Section 4.6). Naltrexone / bupropion should not be used during pregnancy or in women currently attempting to become pregnant. Pregnancy, Lactation, and Fertility will be monitored as part of the routine pharmacovigilance programme for NB. Upon receipt of a case detailing an exposure during pregnancy, the initial information is databased in an Argus case file. As a part of the initial case processing, a follow-up letter containing requests for specific details is mailed to the patient. Obtaining contact information for the patient's physician along with permission to contact is also attempted during the initial patient contact. In circumstances where the name and contact information of the prescriber and/or the treating obstetrician is available, a follow-up letter along with the same form provided to the patient is also mailed in an attempt to obtain medically confirmed information. The information sought includes information with respect to relevant medial history and previous pregnancies, familial history, concomitant medications, and date of last menstrual period / date of positive pregnancy test / estimated conception date / estimated due date. A component of the initial case processing is to schedule an action item in the database for sending an additional follow-up letter to both patient and the prescribing physician or obstetrician, again with requests for specific details, approximately 1 month subsequent to the estimated delivery date for the child. Those details include relevant details of the pregnancy, information on the outcome of the pregnancy and delivery, and infant details including sex / weight / length / Apgar score at 1 and 5 minutes.
Long-term use/ chronic use beyond 1 year	Evidence source: The combined data from the NB clinical development program and the NB-CVOT study provide substantiating data about the safety and tolerability of prolonged/chronic use of NB as it is expected to be utilized in clinical practice. There is efficacy and safety information for 1 year of use from the Phase 3 studies (see Section SIII.2). Population in need of further characterisation: Even supplemented by NB-CVOT data, long term use beyond 1 year remains missing information and will continue to be further assessed when data from a second planned CVOT study become available and using post-marketing data. The SmPC for NB states in Section 4.2 that the need for continued treatment should be evaluated after 16 weeks and re-evaluated annually.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Seizures • Interaction with MAOIs, opioids, drugs that inhibit, induce or are substrates of CYP2B6, and drugs metabolised by CYP2D6 • Increases in blood pressure or heart rate • Hypersensitivity reactions, including severe cutaneous adverse reactions [Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP)] • Neuropsychiatric symptoms • Hepatotoxicity • Use in patients with hepatic impairment • Use in patients with severe or moderate 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 use /chronic use beyond 1 year

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires are available for use during pregnancy: The information sought includes information with respect to relevant medical history and previous pregnancies, familial history, concomitant medications, and date of last menstrual period / date of positive pregnancy test / estimated conception date / estimated due date. Approximately 1 month subsequent to the estimated delivery date for the child the same follow-up questionnaire is utilized to obtain relevant details of the pregnancy, information on the outcome of the pregnancy and delivery, and infant details including sex / weight / length / Apgar score at 1 and 5 minutes.

III.2 Additional pharmacovigilance activities

Study short name and title:

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

Drug utilisation and safety study of Mysimba/Contrave) in Europe and the United States.

Rationale and study objectives:

The European Medicines Agency (EMA) requested that Orexigen provide additional information on the utilisation of Mysimba in Europe and gather further data relating to safety concerns of Mysimba use. As a supplement to the Mysimba Risk Management Plan (RMP), Orexigen has designed this database study to address that request.

This study will describe the utilization and safety of NB in a real-world setting using electronic health records (EHR) and administrative health claims in several European countries and the US. Available characteristics of patients initiating NB will be described, with particular focus on patients receiving NB in a manner non-compliant with the Summary of Product Characteristics (SmPC) at initiation, such as use inconsistent with labelled indication or use in patients with a contraindication to the medication. Examples of use inconsistent with labelled indication may include but are not limited to: age <18 years or use for a reason other than management of weight in a patient who has obesity or is overweight. Examples of contraindications include but are not limited to: current diagnosis of uncontrolled hypertension, seizure disorder, or end-stage renal failure; history of seizures, bipolar disorder, anorexia nervosa or bulimia; current dependence on chronic opioids or opiate agonists (e.g., methadone); current state of acute opiate withdrawal; or any concomitant treatment containing bupropion, naltrexone, or a monoamine oxidase inhibitor (MAOI).

Safety concerns addressed: Seizures, drug interactions, suicidality (i.e., suicidal ideation, attempted suicide or completed suicide), neuropsychiatric events (i.e., mania or depression), hepatotoxicity, severe hypersensitivity reactions, off label use and abuse potential.

Study design:

The study design is a retrospective cohort of users of NB with 18 months of follow up after NB initiation. This study will describe NB utilisation and incidence of AESIs for users compliant and non-compliant with the SmPC. Several databases for this study will be selected based on the number of NB prescriptions and suitable database availability in each country. It was anticipated that this study would use population-based automated data from three different countries: United Kingdom (UK), Spain and Italy. However, other databases, such as Germany's IMS Disease Analyzer, might be included based on ongoing feasibility analyses.

Preliminary feasibility of databases throughout Europe has been conducted annually in advance of study start. After extensive feasibility assessment, several databases for this study have been identified and accordingly selected based on the number of NB prescriptions and availability of a suitable database in each country: DK, FI, NO, SE. Data from the U.S., which remains the principal geographical region of NB sales and utilization, will also be included in this study. The study will close when final analyses are completed for all databases in which data collection was initiated.

Study population:

The study cohort will consist of all users of NB with at least 12 months of clinical data (baseline period) before the index date (e.g., date of first prescription of NB or date of dispensation, as applicable per database) and 18 months of follow up data from UK, Spain and Italy.

Milestones:

Once feasibility of at least one database has been confirmed, and the full study protocol has been endorsed by PRAC, the study will be initiated.

The US arm of the NB-451 study has been finalised (2023).

Anticipated milestone dates are:

- April 15, 2024 (interim report 1)
- April 15, 2025 (interim report 2)
- December 31, 2025 (final report)

Study short name and title:

Study number and title to be assigned for "revised PPC PASS assessment of effectiveness study"

Rationale and study objectives:

The European Medicines Agency (EMA) requested that Orexigen conduct a survey to evaluate the effectiveness of the revised PPC as a category 3 pharmacovigilance study following distribution of the revised PPC.

Study objectives: to be confirmed

Safety concerns addressed: Seizures, drug interactions, blood pressure/heart rate increases, neuropsychiatric events, hepatotoxicity, use in patients with hepatic impairment, use in patients with severe or moderate renal impairment, suicidality in patients with depression, off label use and abuse potential, use during pregnancy

Study design: to be confirmed

Study population: to be confirmed

Milestones: milestones are subject to completion of the ongoing procedures and agreement with EMA and the PRAC on protocol. Additionally, a reasonable timeframe will be needed post distribution of the revised PPC in order to reliably test effectiveness of the new PPC. Provisional milestones are given below.

- The proposed protocol will be submitted 6 months after all ongoing procedures have been agreed and concluded:
    - EMEA/H/A20/1530/C/003687/0065
    - EMEA/H/C/003687/II/0063
    - EMEA/H/C/003687/II/0066
- Pending timely finalisation of ongoing procedures, revised PPC distribution is foreseen finalised Q4 2025
- Revised PPC PASS assessment of effectiveness study start Q1 2028 (as per GVP Module XVI R3)
- Revised PPC PASS assessment of effectiveness study completion Q3 2028
- Revised PPC PASS assessment of effectiveness study report completion Q4 2028

Study short name and title:

NB-CVOT-3 (INFORMUS): A Phase IV Study to Assess the Effect of Naltrexone Hydrochloride Extended Release (ER) and Bupropion Hydrochloride ER Combination (Contrave®/Mysimba®) on the Occurrence of Major Adverse Cardiovascular Events

Rationale and study objectives:

Study NB-CVOT-3 (INFORMUS) is a category I PASS.

Primary Objective
To evaluate the cardiovascular safety of study subjects receiving NB compared with placebo to rule out excess risk of MACE when given in combination with standard of care (real-world setting) to subjects with obesity or who are overweight and have an increased risk of adverse CV outcomes.

Key Secondary Objectives

- To assess the comparative rates of MACE component events (ie, CV death, non-fatal myocardial infarction (MI), and non-fatal stroke) between study subjects receiving NB compared with placebo.
- To compare rates of MACE between subjects receiving NB compared with placebo in various subgroups (as further defined in protocol)

Safety concerns addressed: RMP safety concern Increases in blood pressure or heart rate

Study design:

This Phase IV study is a multi-centre, prospective, randomized, pragmatic, double-blinded, placebo-controlled trial designed to capture cardiovascular outcomes during the real-world use of NB in individuals who are obese or overweight and have an increased risk of adverse cardiovascular outcomes. Subjects will be randomized 1:1 to receive either NB or placebo. Data collection will occur during in-person clinic visits, and subjects will use an eDiary for daily reporting. The primary endpoints are Major Adverse Cardiovascular Events (MACE), which will be adjudicated by a blinded Clinical Events

Committee. Subjects will be followed for one year after treatment termination. During the study, an independent Data Monitoring Committee (DMC) will complete an unblinded review of data when approximately half of the MACE have been adjudicated. The study will conclude when 212 adjudicated MACE have been reached. The study is ongoing in the USA.

Study population:

The study population will include individuals who have obesity (BMI $\geqslant$30 kg/m^2) or are overweight (BMI ≥27 kg/m^2) with at least 1 weight-related comorbidity, aged 18 and older, are at increased risk of adverse CV outcomes, and are randomized 1:1 to receive either NB or placebo.

Milestones:

Progress reports will be submitted to EU authorities annually:

a) Starting one year after the conclusion of the Article 20 procedure (CHMP opinion)
b) The first annual progress report will include provision of the DMC charter (outlining setup and conduct of the planned DMC analyses)
c) The enrolment rate will be assessed during annual progress reports to ensure timely study completion
d) Number of randomised patients, number and proportion of patients permanently discontinuing treatment, and number and proportion of patients withdrawing consent or lost to follow-up will be provided

Study milestones are given below.

Milestone	**Due Date(s)**
First patient randomized	January 2024
Projected study termination*	Q4 2027
Final Report of Study Results	Q4 2028

*Total MACE events required to terminate study – 212

III.3 Summary Table of additional Pharmacovigilance activities

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
A Phase IV Study to Assess the Effect of Naltrexone Hydrochloride Extended Release (ER) and Bupropion Hydrochloride ER Combination (Contrave®/Mysimba®) on the Occurrence of Major Adverse Cardiovascular Events (NB-CVOT-3, INFORMUS) Study is ongoing.	To evaluate the cardiovascular safety of study subjects receiving NB compared with placebo to rule out excess risk of MACE when given in combination with standard of care (real-world setting) to subjects with obesity or who are overweight and have an increased risk of adverse cardiovascular outcomes.	RMP safety concern: increases in blood pressure or heart rate	First patient randomized Projected study termination Final Report of Study Results Annual status reports	January 2024 Q4 2027 Q4 2028 Starting one year after the conclusion of the Article 20 procedure (CHMP opinion)
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable	Not applicable	Not applicable	Not applicable	Not applicable

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
An observational database study to identify real-world utilization patterns of Mysimba use among patients who are new users of Mysimba (**NB-451**)	An observational database study to identify: What are the long-term (up to 18 months) real-world utilization patterns of Mysimba use among patients who are new users of Mysimba	Seizures, drug interactions, suicidality (i.e., suicidal ideation, attempted suicide or completed suicide), neuropsychiatric events (i.e., mania or depression), hepatotoxicity, severe hypersensitivity reactions, off label use and abuse potential.	Protocol (Version 4.0) endorsed by PRAC 2023	The US arm of the NB-451 study has been finalised (2023). Anticipated milestone dates are: -April 15, 2024 (interim report 1) -April 15, 2025 (interim report 2) -December 31, 2025 (final report)
Revised PPC PASS assessment of effectiveness study Study in planning phase	To Be Confirmed	Seizures, drug interactions, blood pressure/heart rate increases, neuropsychiatric events, hepatotoxicity, use in patients with hepatic impairment, use in patients with severe or moderate renal impairment, suicidality in patients with depression, off label use and abuse potential, use during pregancy	Protocol to be proposed to PRAC	- The proposed protocol will be submitted 6 months after all ongoing procedures have been agreed and concluded: EMEA/H/A20/1530/C/003687/0065 EMEA/H/C/003687/II/0063 EMEA/H/C/003687/II/0066 - Pending timely finalisation of the start of ongoing procedures, revised PPC distribution is foreseen finalised Q4 2025

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
				- Revised PPC PASS assessment of effectiveness study start Q1 2028 (as per GVP Module XVI R3) - Revised PPC PASS assessment of effectiveness study completion Q3 2028 - Revised PPC PASS assessment of effectiveness study report completion Q4 2028 data collection.

Part IV: Plans for post-authorisation efficacy studies

Over the course of the NB clinical development programme, a total of 24 prospective human trials (15 Phase 1, five Phase 2, and four Phase 3 trials) were completed. In total, 4,754 subjects were included in the primary analysis dataset from NB clinical trials and were followed for a median of 55 weeks (3,250 person-years). The 1,515 placebo subjects form the basis of the unexposed comparator population, contributing to 1,081 person-years of follow-up.

The clinical trials evidence that supports NB includes a broadly representative selection of obese subjects and includes subjects with both uncomplicated and complicated obesity, such as those suffering from type 2 diabetes mellitus. These trials generally included a broad cross section of the obese population in the development programme along with two different approaches to weight management.

Overall, the trials conducted as part of the NB clinical development programme represent the target population of interest (obese adults) where the drug was administered in a similar manner as it would be expected in a real-world setting and for a duration of up to 1 year. Therefore, further evaluation of efficacy in the post-marketing setting is not warranted at this time.

Table Part IV.1: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

No post authorisation efficacy studies are planned.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	**Routine risk minimisation activities**
Seizure	Routine risk communication: *SmPC*: sections 4.3, 4.4, 4.5, 4.8 and 4.9 PL: sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: 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). Other routine risk minimisation measures beyond the Product Information: Pack size: Mysimba is administered in blister packs which can help reduce the likelihood of medication dosing errors including overdose and the dose-related risk of seizures. Legal status: Mysimba is subject to medical prescription.

Safety concern	**Routine risk minimisation activities**
Interaction with MAOIs, opioids, drugs that inhibit, induce or are substrates of CYP2B6, and drugs metabolised by CYP2D6	Routine risk communication: *SmPC: sections* 4.3, 4.4, 4.5 and 4.8 PL: sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: When opioid use is suspected, a test may be performed to ensure clearance of opioid medication before starting treatment with NB. NB 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. In patients requiring intermittent treatment with opioids (e.g., due to a surgical procedure), NB therapy should be discontinued for a minimum of 3 days before and the opioid dose should not be increased above the standard dose. Other routine risk minimisation measures beyond the Product Information: None. Legal status: Mysimba is subject to medical prescription.

Safety concern	**Routine risk minimisation activities**
Increases in blood pressure or heart rate	Routine risk communication: SmPC: sections 4.2, 4.3, 4.4 and 4.8 PL: sections 1, 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk:

Safety concern	**Routine risk minimisation activities**
	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). Annual assessment of weight loss maintenance and to ensure no adverse change in patient cardiovascular risk (SmPC section 4.2). Other routine risk minimisation measures beyond the Product Information: None. Legal status: Mysimba is subject to medical prescription

Safety concern	**Routine risk minimisation activities**
Hypersensitivity reactions, including severe cutaneous adverse reactions [Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP)]	Routine risk communication: SmPC: sections 4.3, 4.4 and 4.8 PL: sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Advise patients of signs and symptoms and monitor closely for skin reactions; withdraw product immediately in case of signs and symptoms suggestive of these reactions. If patient develops a serious reaction such as SJS and AGEP the treatment must not be restarted at any time. Other routine risk minimisation measures beyond the Product Information: None Legal status: Mysimba is subject to medical prescription

Safety concern	**Routine risk minimisation activities**
Neuropsychiatric symptoms	Routine risk communication: SmPC: sections 4.3, 4.4, 4.8 PL: section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None. Legal status: Mysimba is subject to medical prescription

Safety concern	**Routine risk minimisation activities**
Hepatotoxicity	Routine risk communication: SmPC: sections 4.4, 4.8 and 5.3 PL: section 4

Safety concern	**Routine risk minimisation activities**
	Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None. Legal status: Mysimba is subject to medical prescription

Safety concern	**Routine risk minimisation activities**
Suicidality in patients with depression	Routine risk communication: SmPC: sections 4.4 and 4.8 PL: sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: 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.) Other routine risk minimisation measures beyond the Product Information: None. Legal status: Mysimba is subject to medical prescription.

Safety concern	**Routine risk minimisation activities**
Off-label use and abuse potential	Routine risk communication: The SmPC clearly states the indication for use. SmPC: sections 4.1, 4.2, 4.3 and 4.4 PL: sections 1, 2, and 3 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None. Legal status: Mysimba is subject to medical prescription.

Safety concern	**Routine risk minimisation activities**
Congenital malformations	Routine risk communication: SmPC: sections 4.6 and 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None. Legal status:

Safety concern	**Routine risk minimisation activities**
	Mysimba is subject to medical prescription.

Safety concern	**Routine risk minimisation activities**
Use during pregnancy	Routine risk communication: SmPC: sections 4.6 and 5.3 PL: section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None. Legal status: Mysimba is subject to medical prescription

Safety concern	**Routine risk minimisation activities**
Data on long-term / chronic use beyond 1 year	Routine risk communication: SmPC: section 4.2 PL: section 3 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None. Legal status: Mysimba is subject to medical prescription

Safety concern	**Routine risk minimisation activities**
Use in patients with hepatic impairment	Routine risk communication: SmPC: sections 4.2, 4.3, 4.4 and 5.2 PL: sections 2 and 3 Routine risk minimisation activities recommending specific clinical measures to address the risk: 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). Other routine risk minimisation measures beyond the Product Information: None. Legal status: Mysimba is subject to medical prescription

Safety concern	**Routine risk minimisation activities**
Use in patients with severe or moderate renal impairment	Routine risk communication: SmPC: sections 4.2, 4.3, 4.4 and 5.2 PL: sections 2 and 3 Routine risk minimisation activities recommending specific clinical measures to address the risk: 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 naltrexone/bupropion Other routine risk minimisation measures beyond the Product Information: None. Legal status: Mysimba is subject to medical prescription

V.2. Additional Risk Minimisation Measures

Routine risk minimization activities as described in Part V.1 are generally sufficient to manage the safety concerns of this fixed combination medicinal product with no new active substance, where the originator medicinal products have been on the market for roughly 3 decades.

However, as this fixed combination has a therapeutic indication outside the typical clinical situations in which the mono components are used, a Physician Prescriber Checklist (PPC) has been developed and implemented. The PPC is used to facilitate patient selection when initiating therapy or repeat prescription is issued, as appropriate. The checklist should remind prescribers of the therapeutic indication, as well as contraindications, warnings and precautions needed to select the appropriate patients in which the use of this medicinal product is appropriate.

Additionally, a patient card is being introduced as an educational tool for patients taking NB. This card aims to remind patients to inform their healthcare professionals about their NB use and highlight the precautions related to potential interactions between the naltrexone component and opioid medications.

Name of the additional Risk Minimisation Activity:

Physician Prescribing Checklist

Objective:

The risk minimization tool is a checklist to help doctors assess the suitability of patients for whom NB might be prescribed. This will help prevent patients at an increased risk of side effects, or who are outside the approved indication, from being prescribed NB, both at time of first prescription, at 16-weeks and at annual assessments.

Rationale for the additional risk minimisation activity:

The most important safety concerns for NB are seizures, drug interactions, increases in blood pressure or heart rate, neuropsychiatric symptoms, hepatotoxicity, suicidality in patients with depression, off-label use and abuse potential, use in patients with hepatic impairment/severe or moderate renal impairment. The main risk minimisation strategy is to prevent patients with an increased risk of these adverse drug reactions, in the light of these safety concerns, being incorrectly prescribed NB.

Target audience and planned distribution path:
All physicians who are likely to prescribe Mysimba will be provided with copies of the PPC and the SmPC immediately prior to launch of the product in each member state and at time of update to PPC content, ready for use before and during treatment of a patient with Mysimba.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Studies NB-452 and NB-453 are completed. Further plans to evaluate effectiveness, in the form of revised PPC PASS assessment of effectiveness study, to be deferred until completion of procedures EMEA/H/C/003687/II/0066, EMEA/H/C/003687/II/0063 and EMEA/H/A-20/1530/C/003687/0065.

Fits (Seizures)

Checklist for doctors to be filled in before NB is prescribed to each patient
Objective and rationale • To remind doctors that patients with fits or a history of fits should not be prescribed NB • To remind doctors that patients with a known brain tumour should not be prescribed NB • To educate and remind doctors about additional risk factors for fits • To remind doctors about other medicines which may make fits more likely • To provide an aide memoire to ensure appropriate patient selection

Interaction with other medicines

Checklist for doctors to be filled in before NB is prescribed to each patient
Objective and rationale • To remind and inform doctors about medicines which should not be prescribed at the same time as NB • To warn about other medicines which may make fits more likely

Increases in blood pressure or heart rate

Checklist for doctors to be filled in before NB is prescribed to each patient
Objective and rationale • To remind doctors that patients with uncontrolled high blood pressure shouldn't be prescribed NB • To remind doctors of the potential risk of increased blood pressure for patients treated with NB whose hypertension is controlled • To provide an aide memoire to ensure appropriate patient selection

Mental illness with strange or disturbing thoughts or moods (Neuropsychiatric symptoms)

Checklist for doctors to be filled in before NB is prescribed to each patient
Objective and rationale • To remind doctors that patients with bipolar disorder (people who have moods which swing between episodes of depression and mania when they feel very high and overactive) should not be prescribed NB. Checklist for doctors to inform and educate them about the identified risk of mental illness associated with the use of NB • To reinforce what NB is used for • To educate and remind doctors that patients who have depression or a history of mania should only be prescribed NB if the expected benefits outweigh the possible risks about additional risk factors for mental illness • To provide an aide memoire to ensure appropriate patient selection

Undesirable effects on the liver (hepatotoxicity)

Checklist for doctors to be filled in before NB is prescribed to each patient

Objective and rationale
• To remind doctors
  ○ that patients with severe liver disorders should not be prescribed NB
  ○ that NB is not recommended in patient with moderate hepatic impairment
  ○ that for patients with mild hepatic impairment dose adjustment of NB is necessary
• To provide an aide memoire to ensure appropriate patient selection

Suicidality in patients with bipolar disorder or depression

Checklist for doctors to be filled in before NB is prescribed to each patient
Objective and rationale

Checklist for doctors to be filled in before NB is prescribed to each patient
• To remind doctors that patients with bipolar disorder (people who have moods which swing between episodes of depression and mania when they feel very high and overactive) should not be prescribed NB • To remind doctors that patients with depression or with a history of suicidal thoughts/ suicide attempt should only be prescribed NB if the expected benefits outweigh the possible risks • To provide an aide memoire to ensure appropriate patient selection

Use in patients with severe or moderate kidney disease

Checklist for doctors to be filled in before NB is prescribed to each patient
Objective and rationale • To remind doctors that patients with end stage kidney disease or severe kidney disorders should not be prescribed NB • To remind doctors that, in patients with moderate or severe kidney disorders, dose adjustment is necessary, and that NB should only be prescribed if the expected benefits outweigh the possible risks • To remind doctors to test kidney function for patients at elevated risk for poor kidney function, in particular, individuals with diabetes or elderly individuals, prior to starting naltrexone / bupropion • To provide an aide memoire to ensure appropriate patient selection:

Patient Card

Objective:

To remind patients to inform their healthcare professionals that they are taking NB. This educational tool aims to enhance awareness about the precautions needed when using NB along with opioid medications due to potential interactions. By providing this information, the patient card seeks to minimise the potential risks associated with concomitant use of NB with opioids.

Rationale for the additional risk minimisation activity:

To further address beyond routine measures the important identified risk for NB of interaction with opioids.

Target audience and planned distribution path:

All patients treated with Mysimba will be provided a patient card (with each pack of Mysimba). The agreed content is given in Annex III A of the Product Information.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Routine pharmacovigilance

Direct Healthcare Professional Communication (DHPC)

Objective:

To inform DHPC recipients in the EEA on the undetermined long term cardiovascular risk and provide them new recommendations on annual assessment.

Rationale for the additional risk minimisation activity:

Whilst awaiting finalisation of currently ongoing study NB-CVOT-3 (INFORMUS), to inform DHPC recipients on long term cardiovascular risk and remind them that patients on NB should have their treatment re-evaluated annually.

Target audience and planned distribution path:

All physicians who are likely to prescribe Mysimba; the target group should be further defined at national level, in agreement with the respective national competent authority.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Routine pharmacovigilance.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Seizures	Routine risk minimisation measures: SmPC Section 4.3, 4.4, 4.5, 4.8, 4.9 and Section 2 & 4 of the PL. Pack size: Mysimba is administered in blister packs which can help reduce the likelihood of medication dosing errors including overdose and the dose-related risk of seizures. 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 risk minimisation measures: Physician Prescribing Checklist (PPC). Legal status: Mysimba is subject to medical prescription.	NB-451 Revised PPC PASS assessment of effectiveness study
Interaction with MAOIs, opioids, drugs that inhibit, induce or are substrates of CYP2B6, and drugs metabolised by CYP2D6	Routine risk minimisation measures: SmPC Section 4.3, 4.4, 4.5, and Section 2 of the PL. Specific clinical measures: When opioid use is suspected, a test may be performed to ensure clearance of opioid medication before starting treatment with NB. NB 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. In patients requiring intermittent treatment with opioids (e.g., due to a surgical procedure), NB therapy should be discontinued for a minimum of 3 days before and the opioid dose should not be increased above the standard dose(SmPC section 4.4) Additional risk minimisation measures: PPC, patient card Legal status: Mysimba is subject to medical prescription.	NB-451 Revised PPC PASS assessment of effectiveness study
Increases in blood pressure or heart rate	Routine risk minimisation measures: SmPC Section 4.2, 4.3, 4.4, 4.8 and Sections 1, 2 and 4 of the PL.	Revised PPC PASS assessment of effectiveness study NB-CVOT-3 (INFORMUS)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Specific clinical measures to address the risk: 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). Annual assessment of weight loss maintenance and to ensure no adverse change in patient cardiovascular risk. Additional risk minimisation measures: PPC, DHPC Legal status: Mysimba is subject to medical prescription.	
Hypersensitivity reactions, including severe cutaneous adverse reactions [Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP)]	Routine risk minimisation measures: SmPC Section 4.3, 4.4, 4.8 and Section 2 & 4 of the PL. Advise patients of signs and symptoms and monitor closely for skin reactions; withdraw product immediately in case of signs and symptoms suggestive of these reactions. If patient develops a serious reaction such as SJS and AGEP the treatment must not be restarted at any time. Legal status: Mysimba is subject to medical prescription.	NB-451
Neuropsychiatric symptoms	Routine risk minimisation measures: SmPC Section 4.3, 4.4, 4.8 and Section 2 & 4 of the PL. Additional risk minimisation measures: PPC Legal status: Mysimba is subject to medical prescription.	NB-451 Revised PPC PASS assessment of effectiveness study
Hepatotoxicity	Routine risk minimisation measures: SmPC Section 4.4, 4.8, 5.3 and Section 4 of the PL. Additional risk minimisation measures: PPC. Legal status: Mysimba is subject to medical prescription.	NB-451 Revised PPC PASS assessment of effectiveness study

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Suicidality in patients with depression	Routine risk minimisation measures: SmPC Section 4.4, 4.8 and Section 2 & 4 of the PL. Specific clinical measures to address the risk: 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 risk minimisation measures: PPC Legal status: Mysimba is subject to medical prescription.	NB-451 Revised PPC PASS assessment of effectiveness study
Off-label use and abuse potential	Routine risk minimisation measures: SmPC Section 4.1, 4.2, 4.3, 4.4, and Sections 1, 2, and 3 of the PL. Additional risk minimisation measures: PPC. Legal status: Mysimba is subject to medical prescription.	NB-451 Revised PPC PASS assessment of effectiveness study
Congenital malformations	Routine risk minimisation measures: SmPC Section 4.6 & 5.3 Legal status: Mysimba is subject to medical prescription.	None
Use during pregnancy	Routine risk minimisation measures: SmPC Section 4.6, 5.3 and Section 2 of the PL. Legal status: Mysimba is subject to medical prescription.	Specific follow-up forms are utilized to obtain medical and familial history, as well as perinatal and delivery details. Revised PPC PASS assessment of effectiveness study
Data on long-term / chronic use beyond 1 year	Routine risk minimisation measures: SmPC Section 4.2 and Section 3 of the PL. Legal status: Mysimba is subject to medical prescription.	None
Use in patients with hepatic impairment	Routine risk minimisation measures: SmPC Section 4.2, 4.3, 4.4, 5.2, and Sections 2 and 3 of the PL. Specific clinical measures to address the risk: 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). Additional risk minimisation measures: PPC Legal status: Mysimba is subject to medical prescription.	Revised PPC PASS assessment of effectiveness study

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Use in patients with severe or moderate renal impairment	Routine risk minimisation measures: SmPC Section 4.2, 4.3, 4.4, 5.2, and Sections 2 and 3 of the PL. Specific clinical measures to address the risk: 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. Additional risk minimisation measures: PPC Legal status: Mysimba is subject to medical prescription.	Revised PPC PASS assessment of effectiveness study

Part VI: Summary of the risk management plan

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, opioids, drugs that inhibit, induce or are substrates of CYP2B6, and drugs metabolised by CYP2D6 • Increases in blood pressure or heart rate • Hypersensitivity reactions, including severe cutaneous adverse reactions [Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP)] 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). Bupropion HCl historical experience 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. Naltrexone HCl historical experience 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 4.3). 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 Revised PPC PASS assessment of effectiveness study

Important Identified Risk – INTERACTION WITH MAOIS, OPIOIDS, 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 (including intra-/post-operative opioid analgesia), and patients with opioid dependence.
Risk minimisation measures	**Routine risk minimisation measures** SmPC includes on the list of contraindications (Section 4.3) patients receiving concomitant MAOIs, 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. The SmPC also includes text regarding patients receiving opioids in Section 4.4 "Special warnings and precautions for use" and Section 4.5. 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 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;* *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 MAOIs and regarding opioids in Sections 2 and 4. Mysimba is subject to medical prescription. **Additional risk minimisation measures** Physician educational material, to reinforce indication and ensure appropriate patient selection, which contains, as relevant per national regulatory requirements: -SmPC -Physician Prescribing Checklist

	Patient card
Additional pharmacovigilance activities	NB-451 Revised PPC PASS assessment of effectiveness study

Important Identified Risk – 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. In the integrated summary of the clinical trials supporting the registration of NB, minimal changes in mean resting pulse rate were observed for subjects in all groups over time. An analysis using pre-specified criteria for pulse showed a higher incidence of pulse increases in the Total NB group compared with the Placebo group. An analysis for pulse showed a higher incidence of pulse increases in the NB group compared with the Placebo group. In subgroup analyses evaluating prespecified criteria for pulse, neither race, ethnicity, baseline antihypertensive medication use, nor baseline obesity class had a consistent effect. A generally higher incidence of subjects experiencing increases in pulse was apparent in males and younger subjects in both the NB and Placebo groups. Subjects receiving NB and having a $\geqslant$5% weight loss at endpoint also showed increased incidence in the prespecified criteria for pulse, the opposite pattern was observed in the Placebo group. Overall in the NB clinical trials, a placebo corrected mean increase from baseline in systolic and diastolic blood pressure of up to 1 mm Hg was observed. Mean systolic and diastolic blood pressure showed initial increases of approximately 1 mm Hg in the NB group at Weeks 4 and 8. After this, both mean systolic and diastolic blood pressure began to decrease at each timepoint to Week 28 (systolic) and Week 24 (diastolic) after which, changes in blood pressure from baseline were maintained at approximately 1 mm Hg below baseline values (for each). In the Placebo group, mean systolic blood pressure decreased from baseline over time at each endpoint reaching an average of -2.2 mm Hg below baseline. In a subgroup analysis evaluating prespecified criteria for systolic blood pressure, neither obesity class nor having a $\geqslant$5% weight loss at endpoint had a consistent effect in NB-treated subjects. Small increases in the incidence of subjects experiencing increases in the prespecified criteria for systolic blood pressure were apparent in males, non-Hispanics and subjects using antihypertensive medication in both the Total NB and Placebo groups. Blacks/African Americans showed somewhat higher incidences of prespecified systolic blood pressure criteria compared to other races, and systolic blood pressure showed a trend of increasing with age in NB-treated subjects; no consistent trend was observed for either race or age in the Placebo group. Non-smoking subjects receiving NB also showed slightly higher incidences in the prespecified criteria for systolic blood pressure, the opposite pattern was observed in the Placebo group. Overall, a greater percentage of subjects experienced Blood Pressure and Pulse TEAEs in the NB group compared with the Placebo group (5.9% and 4.2%, respectively). The majority of the events were reported within the Hypertension subtopic (5.3% NB

	and 4.0% Placebo); all other subtopics (Hypotension, Bradycardia, and Tachycardia) had a similar incidence of events in the Total NB and Placebo groups. No Blood Pressure or Pulse-related SAEs were reported in either the Primary or Overall datasets.
Risk factors and risk groups	Risk groups or risk factors associated with 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 on annual assessment to ensure maintenance of weight loss and no adverse change in patient cardiovascular risk in Section 4.2 (Posology and method of administration), as well as text on hypertension in, Section 4.4 (Special warnings and precautions for use), and Section 4.8 (Undesirable effects). The package leaflet includes the following text in Sections 1 and 2: - *… 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.* - *Do not take NB:* - *if you have an abnormally high blood pressure (hypertension) that is not controlled using a medicinal product* Mysimba is subject to medical prescription. **Additional risk minimisation measures** - Physician educational kit, to reinforce indication and ensure appropriate patient selection, which contains: o SmPC o Physician Prescribing Checklist (PPC) - DHPC to prescribers of NB
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). Annual assessment (SmPC section 4.2).
Additional pharmacovigilance activities	Revised PPC PASS assessment of effectiveness study NB-CVOT-3 (INFORMUS)

Important Identified Risk – HYPERSENSITIVITY REACTIONS, INCLUDING SEVERE CUTANEOUS ADVERSE REACTIONS [STEVENS-JOHNSON SYNDROME (SJS), ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS (AGEP)]	
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. In the integrated summary of the clinical trials supporting the registration of NB, the incidence of Hypersensitivity Reaction/Skin

	Rash events was similar in the NB group compared with the Placebo group (13.4% and 15.2%, respectively) in the Primary Dataset and there was no difference in the incidence of SAEs (⩽0.1% in both groups), and the percentage of subjects who discontinued due to these events was also similar (NB 1.9% and Placebo 1.2%). Among the subjects who reported Hypersensitivity Reaction/Skin Rash events as a TEAE, initial onset was observed within the first 8 weeks in approximately half of subjects in the NB group and approximately one third of subjects in the Placebo group. The median time to onset for Hypersensitivity Reaction/Skin Rash events was shorter in the NB group compared to Placebo (7 vs. 15 weeks, respectively). The median duration of Hypersensitivity Reaction/Skin Rash events was 2 weeks in both the Total NB group and the Placebo group. There was no difference in the cumulative probability of reporting Hypersensitivity Reaction/Skin Rash between the Total NB and Placebo groups. In relation to AGEP in particular, for the mono-component bupropion, the product information was updated for the mono-component buproprion to include AGEP as a reaction (4.8), with warning & precaution text in SmPC 4.4. For NB, a low number of probably or possibly related cases have been reported.
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, including severe cutaneous adverse reactions such as SJS and AGEP 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 Revised PPC PASS assessment of effectiveness study

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 Revised PPC PASS assessment of effectiveness study

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 Section 2: 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 **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 Revised PPC PASS assessment of effectiveness study

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. **Additional risk minimisation measures** Physician educational kit, to reinforce indication and ensure appropriate patient selection, which contains: • SmPC • Physician Prescribing Checklist
Additional pharmacovigilance activities	Revised PPC PASS assessment of effectiveness study

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 (⩽ 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. Bupropion HCl historical experience 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 Revised PPC PASS assessment of effectiveness study

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 ⩽ 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 Revised PPC PASS assessment of effectiveness study

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
Additional pharmacovigilance activities	Revised PPC PASS assessment of effectiveness study

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-3 (INFORMUS) is a condition of the marketing authorisation:

A Phase IV Study to Assess the Effect of Naltrexone Hydrochloride Extended Release (ER) and Bupropion Hydrochloride ER Combination (Contrave®/Mysimba®) on the Occurrence of Major Adverse Cardiovascular Events (NB-CVOT-3, INFORMUS).

Study is ongoing.

The purpose of the study is to evaluate the cardiovascular safety of study subjects receiving NB compared with placebo to rule out excess risk of MACE when given in combination with standard of care (real-world setting) to subjects with obesity or who are overweight and have an increased risk of adverse cardiovascular outcomes.

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 NB in a real-world setting using electronic health records (EHR) and administrative health claims in several European countries (Norway, Sweden, Finland, and possibly Denmark) and the US. Available characteristics of patients initiating NB will be described, with particular focus on patients receiving NB in a manner noncompliant with the SmPC at initiation, such as use inconsistent with labelled indication or use in patients with a contraindication to the medication. This study also plans to evaluate the incidence of adverse events of special interest (AESI) in real-world settings.

Study number and title to be defined: Revised PPC PASS assesssment of effectiveness study
Study design to be defined.

Part VII: Annexes

Table of contents

Annex 4 - Specific adverse drug reaction follow-up forms

Please see the following pages.

[redacted]

Date: [DD-MMM-YYYY] Case File Number: [Case ID]

[First Last Name]
[Street Address]
[City, State, Zip]

Re: Request for Follow-up Information

Patient Initials: [Auto-populated by case information]
Product: Contrave®/Mysimba™ initiated on [DD-MMM-YYYY] for [Indication]
Event(s): [Auto-populated by case information]

Dear [First Last Name],

On behalf of Nalpropion, we would like to thank you for providing us with information on the adverse event(s) experienced after receiving Contrave®/Mysimba™ (naltrexone HCl and bupropion HCl) therapy. We have entered your report into the Nalpropion safety database and we depend on this database to provide accurate and up-to-date information allowing us on an ongoing basis to monitor the safety of our medicines.

In addition to the adverse experiences that you noted following your use of Contrave®/Mysimba™, we are aware that you had exposure to our product while you were pregnant. While there is no information clearly indicating that Contrave®/Mysimba™ causes fetal harm, information is limited on the use of this combination product or the individual components in pregnant females. As noted in the Contrave®/Mysimba™ product information, Contrave®/Mysimba™ is in Pregnancy Category "X" and is contraindicated during pregnancy "because weight loss offers no potential benefit to a pregnant woman and may result in fetal harm. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard of maternal weight loss to the fetus." Therefore, we would like to contact you periodically to collect information about the time you are pregnant, the outcome of the pregnancy, and the health of the newborn child. This additional information will be stored in the Nalpropion safety database to enhance knowledge on this subject and increase the ability to provide more meaningful guidance in the future to the prescribers and the users of our products.

On the following pages is a standard form we use for collecting data on exposure during pregnancy. We would ask that you include your answers on those pages. We also ask that you return your responses in the enclosed return envelope and keep a copy for your records. Please note all information is kept confidential.

Thank you in advance for your assistance.
Sincerely,
[redacted]

Date: [DD-MMM-YYYY] Case File Number: [Case ID]

(i) Follow-Up Questionnaire

Patient Initials: [Auto-populated by case information]
Event(s): [Auto-populated by case information]
Suspect Drug: Contrave (naltrexone HCl/bupropion HCl) Extended Release Tablets

1. PATIENT INFORMATION:

Who was exposed to the medication? (**Please tick one box only**) ☐ Mother or ☐ Father

Mother Date of Birth	Height (cm)	Weight (kg)	Initials:	Country:
Day Month Year				

2. PATIENT HISTORY:

Number of previous pregnancies

Date(s) and outcomes of previous pregnancies:

Any relevant medical history? ☐ No ☐ Yes If yes, give details:

Condition	**Start Date** dd/mmm/yyyy	**Stop Date** dd/mmm/yyyy	**Ongoing**
			❑
			❑
			❑
			❑
			❑

Family history of congenital anomaly/genetic disease? ☐ No ☐ Yes If yes, give details:

Condition	**Start Date** dd/mmm/yyyy	**Stop Date** dd/mmm/yyyy	**Ongoing**
			❑
			❑
			❑
			❑
			❑

3. MEDICATIONS (INCLUDE NB):

List all medications. If this report concerns the father, only record medications taken at estimated time of conception; if this report concerns the mother, enter medications taken at the time of conception and during pregnancy.

Generic drug name	Indication	Dose	Frequency	Route	From dd/mmm/yyyy	To dd/mmm/yyyy	Ongoing
1.							☐
2.							☐
3.							☐
4.							☐
5.							☐
6.							☐
7.							☐
8.							☐

4. PREGNANCY DETAILS:

Date of last menstrual period	**Date of positive pregnancy test**	**Estimated conception date**	**Estimated due date**
day month year	day month year	day month year	day month year

Any problems during pregnancy?
☐ No ☐ Yes If yes, give details:

Any additional information? (extra tests, ultrasounds, etc.)
☐ No ☐ Yes If yes, give details:

5. PREGNANCY OUTCOME:

Outcome Date	**Number of weeks of pregnancy**	**Outcome** *(tick one)*		
day month year		☐ Pregnancy terminated ☐ Spontaneous abortion	→ →	Please provide any relevant details in Narrative section
		☐ Live birth ☐ Still birth	→ →	Complete delivery and infant details below

6. DELIVERY DETAILS:

Delivery Type	**Any problems during delivery**
☐ Vaginal ☐ Caesarean Section	☐ No ☐ Yes If yes, give details:

7. INFANT DETAILS:				
Sex: ☐ M ☐ F	Weight (kg)	Length (cm)	Apgar score At 1 minute	Apgar score At 5 minutes

Any noticeable abnormalities at birth? ☐ No ☐ Yes If yes, give details in narrative section below

Any noticeable abnormalities at 1 month post-partum? ☐ No ☐ Yes If yes, give details in additional comments section below

8. ADDITIONAL COMMENTS:

9. REPORTER DETAILS:		
Reporter type: ☐ Investigator ☐ Physician ☐ Pharmacist ☐ Consumer ☐ Other Specify:	Name of person completing the form: (PRINT NAME)	
	Address of person completing the form:	
	Signature of person completing the form:	
	Date form was completed (ddmmmyyyy):	
	Telephone Number:	
	Email Address or Fax number:	

Nalpropion PHARMACEUTICALS

[redacted]

Date: [DD-MMM-YYYY] Case File Number: [Case ID]

[First Last Name]
[Street Address]
[City, State, Zip]

Re: Request for Follow-up Information

Patient Initials: [Auto-populated by case information]
Product: Contrave®/Mysimba™ initiated on [DD-MMM-YYYY] for [Indication]
Event(s): [Auto-populated by case information]

Dear [First Last Name],

On behalf of Nalpropion, we would like to thank you for the information on the adverse event(s) experienced after receiving Contrave®/Mysimba™ (naltrexone HCl and bupropion HCl) therapy as well as any information on your pregnancy. All information received has been entered into the Nalpropion safety database.

As was mentioned in the initial letter you received from Nalpropion, we would like to contact you periodically to collect information about the time you are pregnant, the outcome of the pregnancy, and the health of the newborn child. At this time, we are asking for any additional information you may be willing to provide. This additional information will be stored in the Nalpropion safety database to enhance knowledge on this subject and increase the ability to provide more meaningful guidance in the future to the prescribers and the users of our products.

On the following pages is a standard form we use for collecting data on exposure to Contrave®/Mysimba™ during pregnancy. We would ask that you include your answers on those pages. We also ask that you return your responses in the enclosed return envelope and keep a copy for your records. Please note all information is kept confidential.

Thank you in advance for your assistance.
Sincerely,
[redacted]

Date: [DD-MMM-YYYY] Case File Number: [Case ID]

(ii) Follow-Up Questionnaire

Patient Initials: [Auto-populated by case information]
Event(s): [Auto-populated by case information]
Suspect Drug: Contrave (naltrexone HCl/bupropion HCl) Extended Release Tablets

1. PATIENT INFORMATION:

Who was exposed to the medication? (**Please tick one box only**) ☐ Mother or ☐ Father

Mother Date of Birth	Height (cm)	Weight (kg)	Initials:	Country:
Day Month Year				

2. PATIENT HISTORY:

Number of previous pregnancies

Date(s) and outcomes of previous pregnancies:

Any relevant medical history? ☐ No ☐ Yes If yes, give details:

Condition	**Start Date** dd/mmm/yyyy	**Stop Date** dd/mmm/yyyy	**Ongoing**
			❑
			❑
			❑
			❑
			❑

Family history of congenital anomaly/genetic disease? ☐ No ☐ Yes If yes, give details:

Condition	**Start Date** dd/mmm/yyyy	**Stop Date** dd/mmm/yyyy	**Ongoing**
			❑
			❑
			❑
			❑
			❑

3. MEDICATIONS (INCLUDE NB):

List all medications. If this report concerns the father, only record medications taken at estimated time of conception; if this report concerns the mother, enter medications taken at the time of conception and during pregnancy.

Generic drug name	Indication	Dose	Frequency	Route	From dd/mmm/yyyy	To dd/mmm/yyyy	Ongoing
1.							☐
2.							☐
3.							☐
4.							☐
5.							☐
6.							☐
7.							☐
8.							☐

4. PREGNANCY DETAILS:

Date of last menstrual period	**Date of positive pregnancy test**	**Estimated conception date**	**Estimated due date**
day month year	day month year	day month year	day month year

Any problems during pregnancy?
☐ No ☐ Yes If yes, give details:

Any additional information? (extra tests, ultrasounds, etc.)
☐ No ☐ Yes If yes, give details:

5. PREGNANCY OUTCOME:

Outcome Date	**Number of weeks of pregnancy**	**Outcome** *(tick one)*		
day month year		☐ Pregnancy terminated ☐ Spontaneous abortion	→ →	Please provide any relevant details in Narrative section
		☐ Live birth ☐ Still birth	→ →	Complete delivery and infant details below

6. DELIVERY DETAILS:

Delivery Type	**Any problems during delivery**
☐ Vaginal ☐ Caesarean Section	☐ No ☐ Yes If yes, give details:

7. INFANT DETAILS:				
Sex: ☐ M ☐ F	Weight (kg) ☐☐	Length (cm) ☐☐	Apgar score At 1 minute ☐☐	Apgar score At 5 minutes ☐☐
Any noticeable abnormalities at birth? ☐ No ☐ Yes If yes, give details in narrative section below Any noticeable abnormalities at 1 month post-partum? ☐ No ☐ Yes If yes, give details in additional comments section below				
8. ADDITIONAL COMMENTS:				
9. REPORTER DETAILS:				

Reporter type:		
☐ Investigator ☐ Physician ☐ Pharmacist ☐ Consumer ☐ Other Specify:	Name of person completing the form: (PRINT NAME)	
	Address of person completing the form:	
	Signature of person completing the form:	
	Date form was completed (ddmmmyyyy):	
	Telephone Number:	
	Email Address or Fax number:	

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

SYNOPSIS OF ADDITIONAL RISK MINIMISATION ACTIVITY FOR NB: PHYSICIAN PRESCRIBING CHECKLIST	
Rationale for additional risk minimisation activities	The most important safety concerns for NB are seizures, suicidality in patients with depression and off-label use. The main risk minimisation strategy is to prevent patients with an increased risk of these adverse drug reactions being prescribed NB. This translates into risk minimisation activities to ensure that: • NB is used within the SmPC indication • Patients with contraindications are not prescribed NB. • Physicians understand which patients (without contraindications) are likely to have additional risk factors for safety concerns and may need additional monitoring/counseling. • The benefit-risk balance is positive at the individual patient level. • To reinforce the indication and warning and precautions in the SmPC and prevent off-label use, a Physician Prescribing checklist is proposed to guide physicians to prescribe appropriately.
Objectives of additional RM activities	• To reinforce the indication in the SmPC and prevent off-label use • To educate and remind physicians about additional risk factors for the key safety concerns • To provide an aide memoire to ensure appropriate patient selection and management at time of first prescription, at 16-weeks,and at annual assessments.
Safety concerns of interest	Seizures, drug interactions, increases in blood pressure or heart rate, Neuropsychiatric symptoms, Hepatotoxicity, Suicidality in patients with depression, Off-label use and abuse potential, Use in patients with hepatic impairment/severe or moderate renal impairment..
Description of Additional RM Measures	
Additional RM tools for physicians	Physician Prescribing checklist
Additional RM tools for patients	None
Implementation Plan	
Administration of RM tools	All physicians who are likely to prescribe NB will be provided with copies of the Physician Prescribing checklist and the SmPC immediately prior to launch of the product in each member state. Physicians should complete the checklist for each patient for whom they are intending to prescribe NB or evaluating for treatment with NB and keep the completed form in the patient notes.

SYNOPSIS OF ADDITIONAL RISK MINIMISATION ACTIVITY FOR NB: PATIENT CARD	
Rationale for additional risk minimisation activities	To further address beyond routine measures the important identified risk for NB of interaction with opioids.
Objectives of additional RM activities	To remind patients to inform their healthcare professionals that they are taking NB. This educational tool aims to enhance awareness about the precautions needed when using NB along with opioid medications due to potential interactions. By providing this information, the patient card seeks to minimise the potential risks associated with concomitant use of NB with opioids.
Safety concerns of interest	Interaction with opioids
Description of Additional RM Measures	
Additional RM tools for patients	Patient card 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.
Implementation Plan	
Administration of RM tools	The content is given in Annex III A of Product Information. All patients treated with Mysimba will be provided a patient card (with each pack of Mysimba).

SYNOPSIS OF ADDITIONAL RISK MINIMISATION ACTIVITY FOR NB: DHPC	
Rationale for additional risk minimisation activities	Whilst awaiting finalisation of currently ongoing study NB-CVOT-3 (INFORMUS), to inform DHPC recipients on long term cardiovascular risk and remind them that patients on NB should have their treatment re-evaluated annually.
Objectives of additional RM activities	To inform DHPC recipients in the EEA on the undetermined long term cardiovascular risk and provide them new recommendations on annual assessment.
Safety concerns of interest	Increases in blood pressure or heart rate
Description of Additional RM Measures	
Additional RM tools for physicians	DHPC
Implementation Plan	
Administration of RM tools	All physicians who are likely to prescribe Mysimba will receive the DHPC; the target group should be further defined at national level, in agreement with the respective national competent authority.