DRUG UTILISATION AND SAFETY STUDY OF MYSIMBA/CONTRAVE IN EUROPE AND THE UNITED STATES

Protocol Number:	NB-451
Version:	Draft 4.0
Date: [OBJ]	August 7, 2023

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* Orexigen Therapeutics Ireland Limited (OTIL, based in Dublin Ireland EU) is the Marketing Authorization Holder (MAH) for Mysimba®/Contrave® (naltrexone HCl/ bupropion HCl prolonged-release tablets) and is a subsidiary of Nalpropion Pharmaceuticals LLC., which is headquartered in the United States of America (USA).

PASS Information

Title	Drug Utilisation and Safety Study of Mysimba/Contrave in Europe and the United States
Protocol version identifier	NB-451
Date of last version of protocol	August 7, 2023
EU PAS register number	EUPAS103743
Active substance	ATC code: A08AA62 Prolonged-release Mysimba/Contrave is a fixed-dose combination of naltrexone hydrochloride [HCl] and bupropion HCl
Medicinal product	Mysimba®/Contrave® 8 mg/90 mg prolonged-release tablets
Product reference	EU/1/14/988/001-002
Procedure number	EMEA/H/C/003687/MEA/003.11
Marketing authorisation holder(s)	Orexigen Therapeutics Ireland Limited / Currax Pharmaceuticals, LLC
Joint PASS	No
Research question and objectives	The primary objectives of the study are: 1. To describe demographic and baseline characteristics of patients initiating use of Mysimba/Contrave. 2. To evaluate patterns of Mysimba/Contrave initiation and use, including estimating the number and percentage of patients compliant and non-compliant with the SmPC. The secondary objectives of this study are: 3. To assess and compare the observed incidence AESIs in usual clinical practice among users of Mysimba/Contrave compliant and non-compliant with the SmPC. 4. To assess the proportions of patients in the following groups who are at increased risk for AESI and to describe the characteristics of the patients with AESI: a. Any user of Mysimba/Contrave; b. Users compliant with SmPC; and c. Users out of compliance with SmPC, as described above. 5. To assess the duration of Mysimba/Contrave use. 6. To identify to the extent possible within the data sources: • Initial titration scheme and proportion aligned with SmPC;

	• Dose adjustment in special populations and proportion aligned with SmPC; • Reasons for treatment discontinuation; and • AESIs that may have led to treatment discontinuation.
Country(-ies) of study	Denmark, Norway, Sweden, Finland, U.S.
Authors	Cynthia J Girman, DrPH, FISPE Sydney Thai, PhD Consultants to Currax Pharmaceuticals LLC

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2. ABBREVIATIONS

AESI	Adverse Events of Special Interest
BMI	Body Mass Index
CI	Confidence Interval
EC	Ethics Committee
EMA	European Medicines Agency
EU	European Union
GDPR	General Data Protection Regulation
GVP	Good Pharmacoviglance Practice
ICMJE	International Committee of Medical Journal Editors
MAH	Market Authorisation Holder
MAOI	Monoamine Oxidase Inhibitor
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Regulatory Activities
PRAC	Pharmacovigilance Risk Assessment Committee
SmPC	Summary of Product Characteristics
US	United States

3. DRUG DESCRIPTION

Generic Name: naltrexone hydrochloride and bupropion hydrochloride extended-release tablet

Trade Name: MYSIMBA®/Contrave®

Indications for Use:

Mysimba/Contrave is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:

1. 30 kg/m^2 or greater (obese) or
2. 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia).

Limitations of Use:

1. The effect of Mysimba/Contrave on cardiovascular morbidity and mortality has not been established.
2. The safety and effectiveness of Mysimba/Contrave in combination with other products intended for weight loss, including prescription drugs, over-the-counter drugs, and herbal preparations, have not been established.

4. SYNOPSIS

Title:	Drug Utilisation and Safety Study of Mysimba in Europe and Contrave in the United States
Purpose:	Results from this study will add further definition and clarity to the overall safety profile of Mysimba/Contrave, to inform the MAH's view on the following: 1. to further refine the risk management and pharmacovigilance planning for this product; and 2. to determine whether the SmPC should be revised, based on the available post-marketing evidence, with the objective of optimizing the safe and effective use of the product.
Objectives and Endpoints:	The primary objectives of the study are: 1.To describe demographic and baseline characteristics of patients initiating use of Mysimba/Contrave. 2. To evaluate patterns of Mysimba/Contrave initiation and use, including estimating the number and percentage of patients compliant and non-compliant with the SmPC. The secondary objectives of this study are: 3.To assess and compare the observed incidence of AESIs in usual clinical practice among users of Mysimba/Contrave compliant and non-compliant with the SmPC. 4. To assess the proportions of patients in the following groups who are at increased risk for AESI and to describe the characteristics of the patients with AESI for all users: a. Any user of Mysimba/Contrave; b. Users compliant with SmPC; and c. Users out of compliance with SmPC, as described above. 5. To assess the duration of Mysimba/Contrave use. 6. To identify to the extent possible within the data sources: o Initial titration scheme and proportion aligned with SmPC; o Dose adjustment in special populations and proportion aligned with SmPC; o Reasons for treatment discontinuation; and o AESIs that may have led to treatment discontinuation.
Population:	Users of Mysimba/Contrave with at least 365 days of computerized records prior to first use in Denmark Finland, Norway and Sweden, and other countries (if meeting the threshold for patients and agreed upon

	between EMA and MAH) with sufficient uptake of Mysimba/Contrave in the respective national health systems. Additionally, U.S. data will be included.
Power and Sample Size:	The study will include data from approximately 3,000 patients per database. Only databases with at least 750 patients will be included in the analysis.
Anticipated Study Duration:	3 years (based on current uptake in Denmark, Finland, Norway, and Sweden); study follow-up of 18 months
Treatment:	Mysimba/Contrave
Inclusion/Exclusion Criteria:	Patients will be included in the study if they meet the following inclusion criteria: 1. At least one prescription of Mysimba/Contrave in his/her medical records any time during the study period; 2. At least 365 days of computerized records prior to first prescription/dispensing of Mysimba/Contrave (index date); and 3. Patient is active (i.e., alive and registered/accruing data) at index date. All patients meeting inclusion criteria will be included in the study; no exclusion criteria will be applied.
Safety Assessments:	The incidence rate of adverse events of special interest (AESI) per person-years of exposure after initiation of Mysimba/Contrave will be assessed. Additionally, overall and for each type of AESI, the crude incidence of new AESIs will be reported as the incidence proportion, which will be reported over the empirical follow-up time and with 95% CI.
Data Analysis:	For demographic and baseline variables, descriptive statistics will be used to describe categorical and continuous variables. Descriptive analyses will be performed for all users of Mysimba/Contrave, and by use categories: (1) use inconsistent with the approved indication, and (2) use incompatible with the stated contraindications. The incidence rate (and 95% CI) of new onset comorbidities and concomitant medication after initiation of Mysimba/Contrave will be assessed. Incidence rates will be determined both for the person-years of time exposed to Mysimba/Contrave (i.e., while patient taking medication) after the index date as well as for all person time through 548 days (18 months) after the index Mysimba/Contrave prescription.

	The incidence rate (and 95% CI) of pregnancy and recorded breastfeeding after the Mysimba/Contrave index date will be assessed among females initiating Mysimba/Contrave. The mean, standard deviation, median, mode, and inter-quartile range of Mysimba/Contrave medication duration will be assessed overall and by use categories. Among patients with available information, the proportion of patients with titration and dosing changes in alignment with the SmPC will be calculated.

5. AMENDMENTS AND UPDATES

The NB-451 protocol (V4.0) has been revised to include updated milestones, inclusion of the US data source, Arcadia, and changes to feasibility assessments, now that the NB-451 study is underway.

6. MILESTONES

Milestone	**Nordic Registries Study Anticipated Dates**	**U.S. Study Anticipated Dates**
Study protocol resubmitted to EMA	November 21, 2022	November 21, 2022
Protocol approved by EMA	December 15, 2022*	December 15, 2022*
Registration in EU PAS Register	January 15, 2023	January 15, 2023
Apply for registry data for secondary use	September 15, 2023 (post EC approval)	N/A
Data receipt and start date for data analysis	December 29, 2023	February 15, 2023
Interim report of study results #1**	April 15, 2024	N/A
Interim report of study results #2***	April 15, 2025	N/A
Final report of study results****	December 31, 2025**	August 4, 2023**

* Subsequent dates are dependent on timing of protocol approval by EMA

** Based on counts of patients prescribed/dispensed Mysimba/Contrave through the end of 2021 and assuming both 80% are captured in the databases and 80% of identified patients are new users with at least 365 days continuous eligibility in data source before first Mysimba/Contrave prescription/dispensing, then there should be >3,000 eligible patients in data sources from US, Norway, Finland and possibly Sweden in this

analysis; it is uncertain at this time whether there will be at least 750 patients in Denmark during the conduct of the NB-451 study. Data for this interim study report will be the data available by December 29, 2023; it is likely that data will only be available through 2021 at this time.
*** A second interim report will only be included if Denmark identifies 750-3,000 eligible patients who would be available before December 31, 2024.
**** Final report date dependent on accumulation of data from the four Nordic country databases. Based on counts to date and projections of new users, there should be >3,000 eligible patients in the Norway and Finland data sources at the end of 2023. The 2023 data from Norway and Finland are expected to be available in late 2024.If final data are available in late 2024, the December 2025 final report will include the new final results from Norway, Finland, and Sweden, with updated interim or final analyses in Denmark, if appropriate.. Additionally, the final report will provide synthesis across all four Nordic data sources.

7. RATIONALE AND BACKGROUND

According to the World Health Organisation, weight-related health issues are some of the most significant global public health challenges. Worldwide obesity has nearly tripled since 1975. Obesity (body mass index [BMI] ≥30 kg/m2) and being overweight (BMI ≥27 kg/m2 to <30 kg/m2) are linked to psychosocial conditions and are major risk factors for chronic diseases, including cardiovascular disease, orthopaedic/degenerative joint disease, and diabetes. Globally there are more people who are obese than underweight and this occurs in every region except parts of sub-Saharan Africa and Asia. The World Health Organisation estimates that the prevalence of obesity and overweight, among adult men and women in Europe, is over 20% and over 50%, respectively. The major health risks and complications associated with obesity negatively affect quality of life and reduce average life expectancy. In addition to burdening the health care system, the treatment of overweight and obesity is a public health imperative. Long-term lifestyle changes are essential to mitigate obesity-related morbidity and mortality; however, for overweight and obese individual's lifestyle changes alone are insufficient, and pharmacotherapy should be considered and added.

Mysimba/Contrave, a fixed-dose combination of naltrexone (an opioid receptor antagonist) and bupropion (a selective neuronal re-uptake inhibitor of noradrenaline and dopamine), was approved in Europe for the treatment of adults with a BMI of ≥30 kg/m2 (obese) or ≥27 kg/m2 to <30 kg/m2 (overweight) in the presence of one or more weight-related co-morbidities (e.g., type 2 diabetes, dyslipidaemia, or controlled hypertension).

The European Medicines Agency (EMA) requested that Orexigen Therapeutics Ireland Limited (Orexigen) provide additional information on the utilisation of Mysimba in Europe and further

characterize the safety profile of Mysimba. 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 Mysimba/Contrave in a real-world setting using electronic health records (EHR) and administrative health claims in several European countries and the U.S. Available characteristics of patients initiating Mysimba/Contrave will be described, with particular focus on patients receiving Mysimba/Contrave 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. Use inconsistent with labelled or otherwise authorized indication includes, but is not limited to: age <18 years and use for a reason other than management of weight in a patient who has obesity or is overweight. Contraindications include, but are not limited to, the following: 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).

This study also plans to evaluate the incidence of adverse events of special interest (AESI) in real-world settings. The incidence of seizures, suicidality (i.e., suicidal ideation, attempted suicide or completed suicide), neuropsychiatric events (i.e., mania or depression), hepatotoxicity, or severe hypersensitivity reactions following initiation of treatment with Mysimba/Contrave will be investigated. Additionally, the incidence of AESIs will be evaluated in subgroups of patients, including those who do not adhere to the conditions of use set out in the SmPC.

Results from this study will add further definition and clarity to the overall safety profile of Mysimba/Contrave, to inform the MAH's view on the following:

1. To further refine the risk management and pharmacovigilance planning for this product; and
2. To determine whether the SmPC should be revised, based on the available post-marketing evidence, with the objective of optimizing the safe and effective use of the product.

8. RESEARCH QUESTIONS AND OBJECTIVES

The aim of the study is to assess the long-term (548 days) real-world utilization patterns of Mysimba/Contrave use among patients who are prescribed Mysimba/Contrave. There are no a priori hypotheses for this study.

The primary objectives of the study are:

1. To describe demographic and baseline characteristics of patients initiating use of Mysimba/Contrave; and
2. To evaluate patterns of Mysimba/Contrave initiation and use, including number of prescriptions, number of treatment episodes and duration between prescriptions, as well as estimating the number and percentage of patients compliant and non-compliant with the SmPC.

   Analysis of compliance to the labelled indication and contraindications will be adapted to the specific SmPC for the country relevant to the data source (s). Examples of non-compliance include, but are not limited to:

   Use inconsistent with labelled indication:

   1. Age <18 years
   2. Use other than management of weight
   3. Management of weight in a patient who does not have obesity or is not overweight and has a weight-related comorbidity
   4. A prescribed maintenance dose other than the Mysimba/Contrave 32mg/360mg
   5. Continued use past 16 weeks without ≥5% weight loss

   Use in patients with contraindications:

   6. A current diagnosis of uncontrolled hypertension, seizure disorder (or history of seizures), or end-stage renal failure
   7. A history of bipolar disorder, anorexia nervosa or bulimia
   8. A current dependence on chronic opioids or opiate agonists (e.g., methadone)
   9. A current state of acute opiate withdrawal
   10. Any concomitant treatment containing bupropion, naltrexone, or a MAOI
   11. Patients with a known central nervous system tumour

12. Patients undergoing acute alcohol or benzodiazepine withdrawal
13. Patients with severe hepatic impairment (dependent on local SmPC)

The secondary objectives of this study are:

1. To assess and compare the observed incidence of AESIs in usual clinical practice among users of Mysimba/Contrave compliant and non-compliant with the SmPC. AESIs include new onset of the following:
    1. Seizures
    2. Suicidality (i.e., suicidal ideation, attempted suicide or completed suicide)
    3. Neuropsychiatric events (i.e., mania or depression)
    4. Hepatotoxicity
    5. Severe hypersensitivity reaction
    6. Serotonin syndrome
    7. Major adverse cardiovascular events (i.e., cardiovascular-related death, non-fatal myocardial infarction, or non-fatal stroke)

    Deaths will also be reported in patients in which vital status is known.
2. To assess the proportions of patients in the following groups who are at increased risk for AESI and to describe the characteristics of the patients with AESI in these groups:
    1. Any user of Mysimba/Contrave
    2. Users compliant with SmPC
    3. Users out of compliance with SmPC, as described above
3. To assess the duration of Mysimba/Contrave use
4. To identify to the extent possible within the data sources:
    1. Initial titration scheme and proportion aligned with SmPC
    2. Dose adjustment in special populations and proportion aligned with SmPC
    3. Reasons for treatment discontinuation (not typically available in these databases)
    4. AESIs leading to treatment discontinuation (not typically available in these databases)

9. RESEARCH METHODS

9.1. Study Design

This study will assess a retrospective cohort of users of Mysimba/Contrave with up to 548 days (~18 months) after initiation with treatment with Mysimba/Contrave. This study will describe Mysimba/Contrave utilisation and incidence of AESIs for users compliant and non-compliant with the SmPC.

Preliminary feasibility of databases throughout Europe has been conducted annually in advance of study start. EHR and administrative health databases were assessed in the following countries:

1. Austria
2. Bulgaria
3. Croatia
4. Cyprus
5. Czech Republic
6. Denmark
7. Estonia
8. Finland
9. Germany
10. Greece
11. Hungary
12. Ireland
13. Italy
14. Latvia
15. Lithuania
16. Norway
17. Poland
18. Portugal
19. Romania
20. Slovakia
21. Slovenia
22. Spain
23. Sweden
24. United Kingdom
25. EU-wide IQVIA administrative health data platform

The sales and estimated number of patients available in databases have been provided to PRAC. After extensive feasibility assessment, several databases for this study have been identified and accordingly selected based on the number of Mysimba prescriptions and availability of a suitable database in each country:

1. Denmark (Danish National Health Registries) - Mysimba not reimbursed
2. Finland (Finnish National Registries) - Mysimba reimbursed but restricted to morbidly obese
3. Norway (Norwegian Health Registries) - Mysimba reimbursed but restricted to morbidly obese
4. Sweden (National Board of Health and Welfare) - Mysimba not reimbursed

These countries make use of record linkage systems where patient level data are matched by cross-referencing de-identified (US) or pseudanomynized (Nordic, Laugersen et al., 2021) data through a unique personal identification number between different registers of interest managed by the respective data controllers in a manner that complies with Regulation 2016/679 or the EU General Data Protection Regulation.

As noted in Mysimba PBRER_10 (dated 10 NOV 2022), no new study countries have been identified since EMA endorsement of the NB-451 study protocol dated 15 NOV 2022. As such, the NB-451 study is not expected to be conducted in additional EU countries, given the need for at least 548 days of availability in the data after the index date of Mysimba first use, and now that the NB-451 study is underway and anticipated to finish by December 2025.

Data from the U.S., which remains the principal geographical region of Contrave sales and utilization, will be included in this study as well as data sources across Europe meeting the feasibility requirements. The study will be completed when final analyses are completed for all databases in which data collection was initiated.

9.1.1. Inclusion Criteria

Patients will be included in the study if they meet the following inclusion criteria:

1. At least one prescription of Mysimba/Contrave in his/her medical records any time during the study period (US) ***OR*** at least one dispensing of Mysimba/Contrave in his/her registry any time during the study period (Nordic);

2. At least 365 days of computerized records prior to first Mysimba/Contrave prescription or dispensing date; and3Patient is active (i.e., alive and registered/accruing data) at the time of the first Mysimba/Contrave prescription or dispensing date.

9.1.2. Exclusion Criteria

All patients meeting inclusion criteria will be included in the study; no exclusion criteria will be applied.

9.2. Setting

The study cohort will consist of all users of Mysimba/Contrave with at least 365 days of database data (baseline period) before the date of first prescription or dispensing of Mysimba/Contrave, as

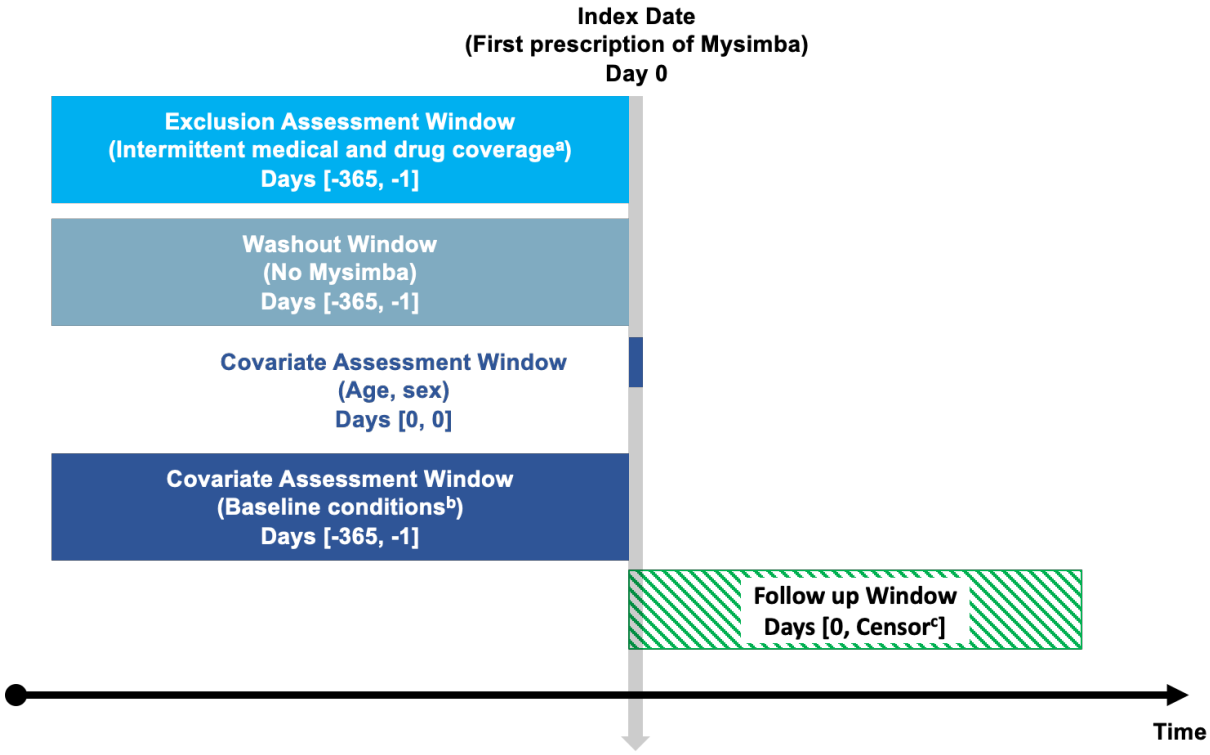
applicable per database (i.e., index date). All available follow-up data up to 548 days after the index date will be included for each patient.

9.3. Variables

9.3.1. Exposure

Exposure to Mysimba/Contrave will be identified through medication prescription or dispensing data (i.e., prescription or dispensing date, dosage [where available], and duration [where available]). The first Mysimba/Contrave prescription after 365 days with no prescription will be the index date, as depicted in Figure 1. All prescriptions of Mysimba/Contrave (or the two component products dispensed within 15 days) during the 548 days (18 months) following the index date will be captured. Patients will be assessed during the entire 548 days following the index date.

Figure 1. Index date, Exclusion and Covariate Assessment, and Follow-up Time for Study



a. Data are 'acceptable for research' for the patient and practice, coverage with computerized records throughout time period with no gaps
b. Baseline conditions included: BMI, height, most recent weight, weight-related comorbidities (e.g., diabetes, dyslipidaemia), neuropsychiatric conditions (mania, bipolar disorder, major depressive disorder [MDD], anorexia nervosa, bulimia), hypertension, end-stage renal disease, seizure disorder, hepatic impairment (defined by Child-Pugh score category), central nervous system tumour, substance use/abuse including acute opiate withdrawal,;uncontrolled hypertension, seizures, bipolar disorder, MDD, anorexia nervosa, or bulimia; use of: naltrexone, bupropion, opioid or opiate agonist, or MAOI; pregnancy, or breastfeeding
c. Earliest of: death, disenrollment, 548 days of follow-up, end of the study period

9.3.1.1. Duration of Mysimba/Contrave Use

Duration of Mysimba/Contrave use will be determined based on prescription or dispensing data (depending on availability in the data source). The days' supply for each prescription will be used to determine the days of medication covered by that prescription. If days' supply is unavailable for a prescription or dispensing, it will be imputed as the mode for the most granular medication variable level available (e.g., by National Drug Code [NDC] in U.S. data, ATC in Nordic data) for the database. The count of duration (days) will include all days during which medication was available without accounting for overlap (i.e., no stockpiling will be included in the duration), a gap of up to half of the days' supply of the immediately preceding prescription, and a wash-out after the end of the last prescription days' supply (Figure 2). After the initial episode of Mysimba/Contrave duration, the duration of any subsequent episodes will also be captured.

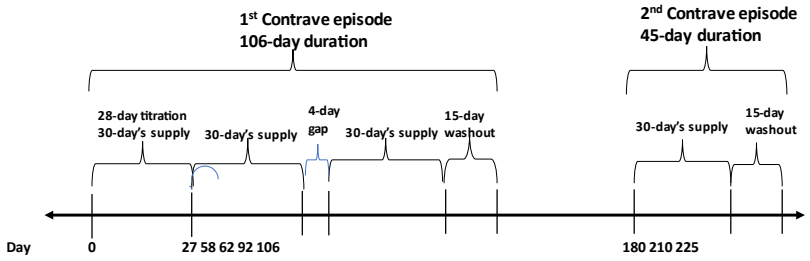
Duration will be assessed in two ways:

1. Continuous treatment in the initial Contrave duration: the number of days duration in the initial Contrave episode (two continuous treatment episodes are in Figure 2; the first is 106 days and the second is 45 days [225-180 days])
2. Total duration of Mysimba/Contrave: the number of days duration in the 548 days (18 months) after the index Mysimba/Contrave prescription (the total duration of Mysimba/Contrave use in Figure 2 is 106+45 =151 days)

   For Mysimba, similar calculations will be done, except that the day's supply will be 28-days after titration.

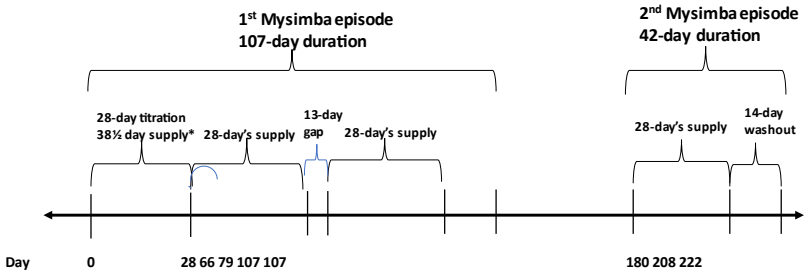
Figure 2. Duration of Mysimba/Contrave Use Episodes

U.S. Contrave



*initial prescription or dispensing is 30-day supply which includes 28 days for titration. Stockpiling will not be accounted for in the analysis

Nordic Countries



*initial prescription or dispensing is 38 ½ day supply which includes 28 days for titration. Each dispensing is 112 pill count. Stockpiling will not be accounted for in the analysis

In addition, the number of prescriptions, number and duration of treatment episodes and duration between treatment episodes will be described.

9.3.1.2. Dosage of Mysimba/Contrave Use

When available, the listed dose of Mysimba/Contrave within each prescription or dispensing will be used as the dose for that patient. However, dose is unlikely to be available in Nordic data and sporadically available in US data. When dose is not provided, then an assumption of the standard dosing (4 pills per day with 32mg naltrexone and 90 mg bupropion in each pill) will be used as the dose for primary analyses. Sensitivity analyses will assign alternate dosing for specific patient groups (see section 9.7.2).

9.3.2. Outcomes

When available, the following variables will be collected after initiation of Mysimba/Contrave (Post-Index Date). A draft listing of variables available in each country is included in Appendix 3 and will be included as final in the Statistical Analysis Plan (SAP).

1. BMI, height, and weight prior to index date, the date of initiation of the medication(s) of interest, (obtained directly from data sources; BMI may be calculated if height and weight available). In the event that BMI and/or weight are not available through licensed access to the Scandinavian National Patient Registries, an attempt will be made to identify the obese population through diagnosis codes or procedures such as counseling for weight loss. It should be noted that this approach may identify a more obese and more motivated population than what would be identified on the basis of BMI. In addition, an approach may be implemented to predict BMI or apply published algorithms predicting BMI. Details will be laid out in the SAP.
2. Weight will be obtained if available 16-24 weeks post-index date to evaluate use inconsistent with labelled indication. BMI after index date will be obtained in the same timeframe, if available.
3. Relevant comorbidities (obtained via ICD-10 codes):
    1. Weight-related comorbidities (i.e., type 2 diabetes, dyslipidaemia, hypertension)
    2. Neuropsychiatric conditions (mania, bipolar disorder, major depressive disorder [MDD], anorexia nervosa, bulimia)
    3. Uncontrolled hypertension
    4. Moderate or severe renal impairment
    5. End-stage renal disease
    6. Seizure disorder
    7. Hepatic impairment (defined by Child-Pugh score category)
    8. Central nervous system tumour
4. Concomitant medication use, including: naltrexone, bupropion, CYP2B6 inhibitors, CYP2B6 inducers, CYP2B6 substrates, CYP2D6 substrates, drugs that lower seizure threshold, opioid or opiate agonist, or MAOI (obtained via ATC [outpatient, Nordic data] or NDC [US data])
5. Pregnancy status and breastfeeding status (obtained via ICD-10 codes)
6. AESIs (obtained via ICD-10 codes):
    1. Seizures

2. Suicidality (i.e., suicidal ideation, attempted suicide or completed suicide)
3. Neuropsychiatric events (i.e., mania or depression)
4. Hepatotoxicity
5. Severe hypersensitivity reaction
6. Serotonin syndrome
7. Major adverse cardiovascular events (i.e., cardiovascular-related death, non-fatal myocardial infarction, or non-fatal stroke)

Deaths will also be described by treatment group, for those with vital status available.

7. Treatment discontinuation (assessed using ATC [outpatient, Nordic data] or NDC [US data])

8. Reason(s) for treatment discontinuation (obtained via ICD-10 codes in the 90 days prior to discontinuation)

All variables will be identified from the data sources via a pre-specified list of definitions (i.e., code lists; see Appendix 2). Occurrence of AESI based on diagnostic codes will be summarized for all patients, and for a subgroup of patients who do not adhere to conditions of the EU SmPC for the Scandinavian countries (adapted to local SmPC as needed) or to the FDA SmPC for the US. Such criteria include: not meeting appropriate criteria for the indication [obese (BMI $\geq$ 30 kg/m^2), or being overweight (BMI $\geq$ 27 kg/m^2 to $<$ 30 kg/m^2) and having at least one weight-related co-morbidity (e.g., type 2 diabetes, controlled hypertension, or dyslipidemia) based on diagnostic codes. If BMI is not available, diagnostic and procedure codes for obesity and weight loss will be applied, recognizing that it will likely produce a more obese population than would be identified by BMI. Subgroup analyses will also be conducted to assess continuous treatment in patients with either renal or hepatic impairment.

Initiation of specific medications that could result with the occurrence of an event corresponding to an AESI (e.g., newly initiating anti-epileptic/seizure medication, newly initiating medications indicated for mania or depression) will also be tabulated. For hepatotoxicity, liver function tests can be used (when available) in addition to diagnostic codes.

For reason(s) patients who discontinue treatment (i.e., do not refill their prescription), events (potential AESIs and contraindications) and clinical status (magnitude of weight loss or gain)

occurring within the 90-day window prior to discontinuation will be summarized. It should be noted that weight may not be available in the Scandinavian registries.

To allow for multiple cycles of Mysimba/Contrave use and assessment of outcomes after initial exposure, the follow-up window for data collection after the index date will be up to 548 days (18 months), as an appropriate time-horizon for this specific purpose. All patient time during the follow-up window will be captured and censoring will occur at the earliest of death, disenrollment, 548 days of follow-up, or end of the study period (December 31, 2023).

9.3.3. Covariates

When available, the following variables needed to conduct analysis for the primary and secondary research objectives will be collected. Variable availability from each country will be summarized in the SAP and is included in Appendix 3 in draft form.

Demographics and Baseline variables (Within 365 days before index date unless otherwise stated below; as depicted in Figure 1):

9. Patient demographics (age and sex on index date) (obtained directly from data source)
10. BMI, height, weight (most recent value on or before the index date) (obtained directly from data sources; BMI may be calculated if height and weight available)
11. Relevant comorbidities (obtained via ICD-10 codes), including:
    1. Weight-related comorbidities (i.e, type 2 diabetes, dyslipidaemia, hypertension)
    2. Neuropsychiatric conditions (mania, bipolar disorder, major depressive disorder [MDD], anorexia nervosa, bulimia)
    3. Uncontrolled hypertension, if possible
    4. Moderate or severe renal impairment
    5. End-stage renal disease
    6. Seizure disorder
    7. Hepatic impairment (defined by Child-Pugh score category, if available)
    8. Central nervous system tumour

12. History of, or current substance abuse/dependencies including acute opiate withdrawal (obtained via ICD-10 codes)
13. History of uncontrolled hypertension, seizures, bipolar disorder, MDD, anorexia nervosa, or bulimia (obtained via ICD-10 codes)
14. Prior medication use, including: naltrexone, bupropion, CYP2B6 inhibitors, CYP2B6 inducers, CYP2B6 substrates, CYP2D6 substrates, Monoamine oxidase inhibitors, Opioids, Opium alkaloids and derivatives and drugs that lower seizure threshold (obtained via ATC [Nordic data] or NDC [US data]) – see Appendix 2 and 2A
15. Pregnancy status and breastfeeding status (obtained via ICD-10 codes)

All variables will be identified from the data sources outlined below using a pre-specified list of definitions per database (Appendix 3), to be defined in the SAP as final.

9.4. Data Sources

Data sources for the study were determined based on the country-specific launch and uptake of Mysimba/Contrave and final assessment of database suitability for conducting this study. Given the need for at least 548 days of availability in the data after the index date of Mysimba first use, and now that the NB-451 study is underway, four European (Norway, Finland, Sweden, and possible Denmark) and one US data source are planned for inclusion in the interim and final study reports.

9.4.1. European Data Sources

The analysis based on the European data sources will complement an analogous methodological approach based on the data source derived from the US to inform the overall safety analysis. After presentation of feasibility results to PRAC, the following data sources are proposed:

1. Denmark (Danish National Health Registries) - Mysimba not reimbursed
2. Finland (Finnish National Registries) - Mysimba reimbursed but restricted to morbidly obese
3. Norway (Norwegian Health Registries) - Mysimba reimbursed but restricted to morbidly obese

4. Sweden (Swedish National Registries) - Mysimba not reimbursed

Currax has engaged a qualified vendor and research partner(s) who will apply for access to the licensed Nordic registry data, following Ethics Committee (EC) approval of the study protocol in each of the Nordic countries. Finalization of the protocol and particularly the SAP will necessitate consideration of specific data fields and variables that are available through this licensing process.

These national, population-based research registries capture population data, health data (including registries of hospital encounters, laboratory results (Denmark only), disease registries), death data, and socioeconomic data within each country. Records cover nearly all citizens and residents in each country throughout their time in the country. The registries have high accuracy and completeness and are maintained electronically (Laugersen et al., 2021). The registries have a strong scientific track record for accurately measuring exposure to prescription medications (Wettermark et al., 2013; Laugersen et al., 2021). Upon obtaining a separate permission, hospital records can be reviewed if necessary for the purposes of validation.

All citizens of these countries are represented in these national registries until death or emigration, providing virtually complete long-term follow-up. Identification of individuals by their unique personal identifier permits linkage to other national health databases (Laugersen et al., 2021). Thus, a large amount of specialized information from specific registries, such as hospitalization, prescription, heart disease, and death registries, can be linked for research (Schmidt 2015; Laugersen et al., 2021). The registries are highly complete and accurate due to the automation of their processes, as well as laws and other incentives motivating healthcare providers to collect and send the data electronically to their national databases (Gribsholt et al., 2019). The data from each country are expected to contain sufficient information to elucidate occurrence and determine levels of all variables, with the following exceptions which may be prone to misclassification due to limited coding in administrative and clinical data: obese or overweight with at least one comorbidity, neuropsychiatric conditions, history or current substance use or dependence, breastfeeding status, initial titration scheme and dose adjustments (expected to be unavailable since only one dose/pack type is available in the Nordic countries and no measure of titration scheme or adherence is included within the data), and reason(s) for medication discontinuation. Any country database with at least 750 patients with at least 365

days of data before the index Mysimba use and at least 548 days of availability in the data after the index date of Mysimba will be evaluated for whether there is sufficient required patient data to conduct this study. If there is sufficient data and uptake indicating that the database will reach more than 3,000 patients within the timespan of this drug utilisation and safety study, then it will be added to the data sources for evaluation. It should be noted that reimbursement varies in Scandinavia, with no reimbursement for Mysimba in Sweden and Denmark, and reimbursement in Norway and Finland restricted to morbidly obese patients who are at higher risk of cardiovascular and other events.

9.4.1.1. Danish National Health Registries

The analysis of the Danish population will be conducted with The Danish National Health registries, which includes data on reimbursed prescription drugs, medical encounter data, and related patient demographic and clinical variables. The National Prescription Registry (NPR), records medicine according to Anatomical Therapeutic Chemical (ATC) classification codes and product codes/names will be used to identify exposure to Mysimba. The NPR includes individual-level data on prescriptions filled by Danish residents at community pharmacies since 1995. The NPR contains 46 variables that describe each prescription, the patient receiving the prescription, the drug dispensed, the prescribing healthcare provider, and the pharmacy dispensing the drug. Additional data will come from the Danish National Patient Registry of hospital encounters, which includes information on diagnoses, selected treatments, and surgical procedures, and occurrence (not results) of diagnostic procedures of residents. The patient registry also includes administrative data consisting of the region the patient's residence, the admitting hospital, any referring healthcare providers or hospitals, reason for going to the hospital, and timing of hospitalization or treatment.

Data can also be linked to the Danish Laboratory Research Database, enabling researchers to further determine diagnoses and conditions through laboratory results. Denmark also has other registries that capture deaths, socioeconomic status, education, income, and social benefit data. Residents are identified and linked to all Danish registries by the Civil Personal Register (CPR) number and demographic information can be obtained from the Danish Civil Registration System. Based on current and projected Mysimba prescription sales and lack of reimbursement for Mysimba in Denmark, we do not anticipate that this database will include > 750 new users

of Mysimba who would be eligible for inclusion in the study as of December 31, 2023. Feasibility counts will be obtained at the time of the first interim report. Analysis of the database will be conducted at the time of interim analyses or final analysis if a total of >750 patients are eligible for study inclusion.

9.4.1.2. Finnish National Registries

The Finland Prescription Register includes data on prescription drugs that were reimbursed through the National Health Insurance Scheme since 2008. The data includes the medicines and corresponding products that have been purchased and reimbursed. The data are classified via the ATC system. Additionally, data will come from the Finnish Care Register for Health Care, which includes data on inpatient care as well as outpatient care. This includes data such as patient identification number, municipal residence, admission and discharge dates, diagnoses, any treatments provided, reason for seeking care, and medical procedures. Finland has other registries that capture social welfare services. All registries can be linked to the Population Register Centre, which contains demographic data on Finnish residents.

This data source was included at the request of the EMA.

Based on current and projected Mysimba prescription counts from the feasibility assessment, restriction of reimbursement of Mysimba to morbidly obese in Finland and assuming patients obtain approximately 6 Mysimba dispensings, 80% of patients are captured in databases and 80% of identified patients are new users with at least 365 days continuous eligibility in data source before first Mysimba prescription/dispensing, we anticipate having more than 750 new users of Mysimba who would be eligible for inclusion in the study as of December 31, 2023. Actual counts will be obtained at the time of the first interim report. Analysis of the database will be conducted at the time of interim analyses or final analysis if >750 patients are eligible for study inclusion, which is expected.

9.4.1.3. Norwegian Health Registries

The Norwegian Prescription Database (NorPD) includes data on all prescription drugs dispensed in Norway since January 1, 2004 and is controlled by the Norwegian Institute of Public Health (NIPH). Pharmacies electronically register prescriptions to the NorPD via Statistics Norway on a monthly basis. The residents' national ID number and the prescribing provider's ID number are

replaced by a pseudonym to link drug use to individuals and other registries data while protecting patient identity. The NorPD will be linked with other Norwegian Patient Registries with information that includes demographic information of the patient (sex, year of birth, and municipality of residence), place and time of treatment, diagnoses, medical procedures, and reimbursement information of medical care.

Based on current and projected Mysimba prescription counts as estimates obtained during the last annual feasibility assessment and reimbursement in Norway restricted to the morbidly obese, we anticipate that this database may include >3,000 new users of Mysimba who will be eligible for inclusion in the study as of December 31, 2023 (to be confirmed when data access is granted). A final analysis of the database will be conducted for the final report including all patients meeting the inclusion criteria for the study as of 31 December 2024 (final report available 31 December 2025).

9.4.1.4. Swedish National Registries

The Swedish Statistical Database for Medicinal Products contains data on all prescription drugs dispensed by pharmacies in Sweden from 2006 – 2020. The registry includes medications and any accompanying consumable products (e.g., food for special nutrition for children under 16 years of age) dispensed to residents of the Kingdom. Included among the data is information on patient information (gender, age, location), product information such as ATC classification codes, pharmaceutical names, and quantity dispensed, when medications were prescribed, costs, and healthcare provider information of who prescribed the drug. These data will be linked with the Swedish Inpatient Registry (or Hospital Discharge Register), which provides data on physical and psychiatric inpatient and hospital-based outpatient care, along with patient related data (including age, sex, county of residence), hospital and department the patient visited, timing and duration of hospitalization and discharge, medical diagnoses, procedures, and psychiatric care.

Based on current and projected Mysimba prescription counts and the lack of reimbursement of Mysimba in Sweden, we anticipate that this database will include > 750 new users of Mysimba who would be eligible for inclusion in the study as of December 31, 2023. Actual counts will be available with the first interim report. Analysis of the database will be conducted for the final report if there are >750 eligible patients at the time of interim or final analyses.

9.4.2. United States Data Source

An EHR or claims-based integrated database across multiple healthcare systems in the United States, providing a representative mix of US Commercial Insurance and Medicare (major systems of health insurance in the US) has been selected. Arcadia Data Research was chosen as the US data for this study because of their approximately ten-year history of successfully curating data for health systems that are substantially involved in value-based care, which necessitates high-quality clinical data across the included patient populations. Data incorporated into the US dataset will include electronic medical records from multiple systems, laboratory test orders, and prescription data. Moreover, a sizeable proportion of the EHR population will also have their health insurance claims records linked in their final (adjudicated) form. The typical data extract will include (but is not limited to): patient demographics and characteristics (including height and weight or BMI if available), medical encounters, appointments, provider data, charges, assessments, immunizations, health maintenance and medical history, laboratory orders/results, vital signs (e.g., blood pressure, heart rate), patient insurance, prescriptions and active medications, problem lists, and patient allergy information. EHR data are sourced from large integrated delivery networks, academic medical centres, ambulatory care, primary care, core hospitals, and others. The data are coded in standard vocabularies used within the US, including ICD-10, NDC, CPT, LOINC, etc. Additional information, such as social determinants of health will be captured, if available. The data are expected to contain sufficient information to elucidate occurrence and determine levels of all variables, with the following exceptions which may be prone to misclassification due to limited coding in administrative and clinical data: neuropsychiatric conditions, history or current substance use or dependence, breastfeeding status, and reason(s) for medication discontinuation.

The integration of claims data for a subset of patients will be important for this study in order to capture pharmacy prescriptions dispensed and for better capture of MACE events. The selected database will be described in more detail in the US SAP.

We anticipate that the US dataset will include >20,000 new users of Contrave who will be eligible for inclusion in the study as of December 31, 2022. The final analysis of the US database will be conducted and presented in a US only study report.

9.5. Study Size and Statistical Power

In the final report from each data source, the study will include data from approximately 3,000 patients per database. Based on the safety profile of bupropion, a sample size of 3,000 with no events of an outcome enables 95% confidence that the chance of that outcome is at most 3 in 3000 (i.e., 1/1000 or 0.1%). As an example, within the integrated summary of safety and effectiveness for Contrave, 13.7% of patients had a treatment emergent adverse event (TEAE) and 0.1% had a treatment emergent serious adverse event (SAE) of hypersensitivity reaction/skin rash (ISS table 2-82). Having 3,000 patients in each database would yield approximately 411 patients with this TEAE and 3 patients SAE. The confidence intervals around both percentages will be approximately 2.5%.

9.6. Data Management

All de-identified (pseudonymized in Nordic countries), inpatient, outpatient and other healthcare-transactional data for patients with at least one prescription of Mysimba/Contrave will be obtained and maintained on a server by an analyst experienced in evaluating that database (patient level data will remain within each country). The data will be stored and accessed according to the sites' data privacy and security practices.

Data management and transformation to analytic datasets from the line-level data will be performed by an experienced analyst. Data extraction, curation of analytic data sets, analysis, and generation of tables and figures will be conducted in accordance with established standard operating procedures at each organization conducting data analysis. Additionally, code will be reviewed by another analyst (or the project director) adept in the coding language and analysis of the data. Face validity of descriptive statistics and incidence rates will be reviewed by the research team.

Management of the US data source will be conducted in accordance with the internal quality management system of the organization conducting the analysis, including integrated Standard Operating Procedures (SOPs) for conducting non-interventional PASS studies with secondary data. Manipulation, housing, and analysis of the US data source will occur within a managed virtual private cloud using native (i.e., secure) Amazon Web Services offerings, including a Postgres(-like) database. Statistical analyses will be conducted, principally, using SAS 9.4. If

necessary, packages from R, Python, or SPSS will be utilized – and such use will be described in the report. No individual data will be downloadable from this cloud environment. For access to the Scandinavian national patient registries, researchers or a vendor located in Scandinavia are required to access data from the registries on secure servers of registry owners.

Applications for data access to the Scandinavian registries in each of the four countries will be pursued once EC approval of the NB-451 protocol is granted in each of the Nordic countries. Aggregated data (output of data analyses) will be saved and stored on secure servers and analyzed using secure systems. Among other things, all employees of the vendor will have a password for the IT system. All work-related material must be saved on a network drive, which is scanned to prevent misuse, and backup happens automatically. Rules also apply to e-mail accounts, PCs and mobile devices.

Any research partner in Nordic countries that applies for access to the Scandinavian patient registries will work according to their legal frameworks and their institutional IT policies.

9.7. Data Analysis

9.7.1. Timing of Feasibility, Interim, and Final Analyses

Prior to study start, feasibility was conducted annually.

One cohort per country will be extracted each time the database is opened. Per database, the following analyses will be conducted:

1. ongoing data review, for each of the participating Nordic countries
2. a first (interim) analysis when a database size reaches 750 patients with up to 548 days of activity in database after index date
3. a second (interim) analysis when an additional 2,250 patients (total 3,000 patients) with a Mysimba/Contrave index date are included in a database with up to 548 days of calendar time available in the database after the index date
4. a final analysis of the database will be conducted for the final report including all patients from the EU data sources meeting the inclusion criteria for the study as of 15 February 2025. If >3000 patients are available at the time of an interim analysis, the final report for

that database will be submitted one year after data is accessible. If final data is available 31 Dec 2024, the final report will be submitted by 31 Dec 2025.

All analyses will be performed separately in each country. All patients in the study will be included in the analysis, regardless of whether there is evidence of any contact with the health system (as registered by any data in the database) after inclusion into the study. One interim and one final analysis will be conducted per country. A final report will be generated when the last database in the study conducts the final analysis (when the last database has >3000 Mysimba patients, or 31 Dec 2025, whichever comes first). The final analysis from the four participating Nordic countries will be included in that report which will be accompanied by synthesis of findings, discussion, and interpretation across all Nordic databases.

9.7.2. Descriptive Statistics

For demographic and baseline variables and duration of Mysimba/Contrave use (measured as both continuous treatment of the initial Mysimba/Contrave duration and the total treatment duration of Mysimba/Contrave), descriptive statistics will be used to describe continuous variables, (e.g., mean, standard deviation, median, quartiles 1 and 3, minimum, maximum, and two-sided 95% confidence intervals [CI]). Categorical variables will be described by the total and percentage of each response and the number of missing data (data that are unavailable in the database).

Patterns of Mysimba/Contrave use will be described by mean (standard deviation, SD) and median (quartile1, quartile 3) number of prescriptions per patient, number and duration of treatment episodes per patient as well as the average duration between prescription episodes. Analyses will be performed for all users of Mysimba/Contrave, including an assessment of whether the subjects have adhered to the prescribed treatment with Mysimba/Contrave according to the terms of the SmPC (adapted to the local country SmPC for the data source as needed, and adapted if BMI is not accessible). The number and proportion of patients who received treatment with Mysimba/Contrave will be provided according to the following subgroups (availability of variables to be summarized in SAP):

(a) Inconsistent with labelled indication:

1) Age <18 years
2) Use other than management of weight
3) Management of weight in a patient who does not have obesity or is not overweight and has a weight-related comorbidity
4) A prescribed maintenance dose other than the Mysimba/Contrave 32mg/360mg
5) Continued use past 16 weeks without ≥5% weight loss

(b) Incompatible with the stated contraindications set out in the SmPC:

1) A current diagnosis of uncontrolled hypertension, seizure disorder (or history of seizures), or end-stage renal failure
2) A history bipolar disorder, anorexia nervosa or bulimia
3) A current dependence on chronic opioids or opiate agonists (e.g., methadone)
4) A current state of acute opiate withdrawal
5) Any concomitant treatment containing bupropion, naltrexone, or a MAOI
6) Patients with a known central nervous system tumour
7) Patients undergoing acute alcohol or benzodiazepine withdrawal
8) Patients with severe hepatic impairment

The proportion of users non-adherent to each component of the indication/contraindications will also be determined. Small numbers will be presented as "<x" where "x" represents the defined threshold for the smallest number of patients that is allowed to be presented from the data source. Since information on the titration scheme is expected to be sparse (and, not present in the Nordic data), a sensitivity analysis will also be conducted where the first dispensing (112 tablets) is allowed to cover the full time of titration (i.e., 7 tablets in first week (n=7 days), 14 tablets in second week, 21 tablets in third week, and the remaining 70 tablets over 17.5 days (4 tablets per day) for a total of 38.5 days). The possible gap will be 19 days (half of the days' supply) before the second dispensing. Duration of Mysimba/Contrave use and adherence will be recalculated based on this adjustment. Adherence to the titration scheme will be confirmed for a patient if the second dispensing occurs within 40 days +/- 7 days from the first dispensing. Additionally, another sensitivity analysis will be implemented in which patients with evidence of renal or liver impairment are allowed up to 56 days for consumption of *each* dispensing to account for

continued use and adherence within these patients who are unlikely to reach the full recommended dosage due to renal or hepatic dosage adjustments.

9.7.3. Incidence Rate of AESIs

The incidence rate of AESIs per person-years of exposure after initiation of Mysimba/Contrave will be assessed. Person-time of exposure will be calculated as the duration from the index date through the date of last Mysimba/Contrave prescription or dispensation (i.e., total treatment duration of Mysimba/Contrave), as applicable, plus 4 weeks. The number of cycles of Mysimba/Contrave during the exposure period will be summarized comparing all users, irrespective of their treatment duration status.
For each type of AESI, the crude incidence of new AESIs will be reported and the incidence proportion and 95% CI of will be estimated as the number of patients experiencing each type of event during Mysimba/Contrave exposure divided by the number of patients initiating treatment with Mysimba/Contrave. The proportion will be reported per 1,000 persons. The incidence density rate and 95% CI of AESI will be reported per 1,000 per person-years, using the sum of the person-years of the at-risk population as the denominator.

Further, clinical events of interest that might be associated with the occurrence of a potential AESI (e.g., newly initiating anti-epileptic/seizure medication, newly initiating medications indicated for mania or depression) will also be tabulated. For hepatotoxicity, liver function tests can be used (when available) in addition to diagnostic codes.

For reason(s) patients who discontinue treatment (i.e., do not refill their prescription), clinical events and health status occurring within the 90-day window prior to discontinuation will be summarized.

9.7.3.1. Incidence Rates of AESIs in Subgroups of Patients

If data are available and appropriate predictors are available in the respective database, sensitivity analyses around the definition of each type of AESI will be performed. Incidence

proportion and density of each type of AESI will also be calculated for the subgroup of patients compliant or non-compliant with the EU SmPC (as listed in section 9.7.1, the criteria will be adapted for the relevant country of the data source stems if the SmPC differ across such countries, i.e., for U.S.), including relevant comorbidities, concomitant medications, and pregnancy. Adaptations will be made if BMI is not available; these will be described in the SAP.
The incidence rate (and 95% CI) of new onset comorbidities and concomitant medication after initiation of Mysimba/Contrave will be assessed. Incidence rates will be determined both for the person-years of time exposed to Mysimba/Contrave (i.e., while patient taking medication) after the index date as well as for all person time through 548 days after the index Mysimba/Contrave prescription.
The incidence rate (and 95% CI) of pregnancy and breastfeeding after the Mysimba/Contrave index date will be assessed among females initiating Mysimba/Contrave. These analyses will be conducted in data sources where the necessary variables are present.

9.7.4. Titration, Change in Dose, and Discontinuation

Among patients with available information, the proportion of patients with titration and dosing changes in alignment with the EU SmPC will be calculated. The local SmPC for the country of the data source may be used, if different than the EU SmPC.
Because reason discontinuation is rarely found in real world data, clinical events of interest and health status occurring within the 90-day window prior to discontinuation will be summarized for patients who discontinue treatment (i.e., do not refill their prescription). However, attribution to product is not possible.

9.7.5. Missing Data

For each database, the number and proportion of patients with missing values for important variables (i.e., patient demographics, history, comorbidities and conditions, or medication) will be reported. If missing values occur in >5% of patients within a database, then each missing data element will be imputed based on the mode of each variable within strata defined by BMI category, age, and sex. In this DUS study, characteristics of individuals with missing information on BMI and weight will be described separately, along with correlates of this missing information. BMI and weight will not be imputed in the primary analysis. Imputed variables will not be used when determining *use inconsistent with labelled indication*.

9.8. Quality Control

The coordinating center QMS integrated SOPs will cover document development, analytic procedures, quality assurance, and archiving of project materials. The US analysis will be conducted under this QMS which is independently assessed against the most recognized and comprehensive international standard for quality management systems, ISO 9001. The QMS complies with the ISO 9001:2015 standard; the ISO 17025:2017 standard; U.S. Code of Federal Regulations, Title 10, Part 50, Appendix B; U.S. Code of Federal Regulations, Title 10, Part 21; and the respective advertising policy for each registration, accreditation, and approval. The quality management processes will be followed for review of materials from the Nordic sites insofar as source data is available from these sites.

DCE works according to its internal SOPs, which have been subject to several external audits, including those from industry and from regulatory agencies. For PASS protocols, we are required to use the EMA-specified template. Studies will be registered in the EU PAS Register. We work according to the principles of the ENCePP Code of Conduct http://www.encepp.eu/code_of_conduct/, specifically referenced in Module VIII of the EMA's GVP (https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices).
Research partners in other Nordic countries will work according to their own SOPs or receive SOPs from the coordinating center.

9.9. Limitations on the Research Methods

9.9.1. EHR and Administrative Claims Data

The measurement of exposure to Mysimba/Contrave in EHR relies on the presence of a prescription for a medication while the exposure in administrative claims data relies on the presence of filled claims for the medication. For these reasons, certain data may not be captured because (a) treatment with Mysimba/Contrave is initiated and managed outside of the nationally reimbursed health system or (b) patients prescribed with Mysimba/Contrave do not take the medication. This may result in the extent of exposure being understated or overstated in the measures based on the duration of exposure used in the analysis.
Key variables such as weight, height, and BMI would not typically be available in administrative claims data. However, due to use of EHR and registers linked to EHR, these key variables are much more likely to be available. Height can be carried forward over an extended period, if needed. Weight is typically present at each clinic visit, which is where the medication would be prescribed, and thus starting weight is likely to be present. In the small number of instances in which weight is not available during the 365 days before the index date, it will be predicted conditional on other baseline variables and previous weight information. A similar approach will be taken for BMI.
Diagnostic codes reflect diagnoses or events that typically result in or are noted during a medical encounter. Those that are not associated with a medical encounter may not be captured.

Assessment after index Mysimba/Contrave prescription will occur both during periods of known use and during the pre-defined exposure period of 548 days after the index prescription. This may lead to attribution of findings to the medication even during periods of non-use.
Additionally, data from clinical practice exhibit more heterogeneity than is seen in clinical trials. Thus, the data in this study are likely to represent a broad variety of patient experiences. The experience of any one individual may not be represented by the averages of the patient population. In addition, subgroups may exhibit different experiences than the overall population of patients taking Mysimba/Contrave.
To date, data sources within Europe other than those in the Nordic countries have not captured adequate numbers of patients for inclusion within this study. The healthcare delivery systems established in the Nordic countries favoring adoption and use of Mysimba/Contrave are different from the other European countries (e.g., Nordic countries include private practice care within available databases). This may explain the differentially lower or no measurable uptake of Mysimba/Contrave to inform the assessment in other countries.
While insufficient data have been identified in other EU data sources, it is important to note that individuals and the health care system in the Nordic countries may not be generaliseable to other EU countries. Thus, data from outside of Europe (i.e., US) have been added to the study..

10. PROTECTION OF HUMAN SUBJECTS

The study will be conducted using industry best practices for conducting secondary data, and specifically pharmacoepidemiologic, research in healthcare databases and electronic medical records. The study will be conducted in compliance with ethical standards as specified by the Declaration of Helsinki (World Medical Association, 9, July 2018). Each country-specific extraction will be conducted within country, by authorized researchers, following approval of the protocol by the designated review board for compliance with ethical standards for secondary research.
Data will be assessed in research-grade, de-identified data sources. Results will be presented in aggregated tables/figures. Small numbers will be presented as applicable for each database (e.g., "<x" will be used where "x" represents the defined threshold for the smallest number of patients that can be presented from the data source) to comply with the EU GDPR and the applicable European or U.S. data privacy rules to render the data subjects potentially re-identifiable by

virtue of special characteristics of the data subjects within the aggregate data. The Sponsor and its vendors will not receive any patient identifiable or identified information at any time during the study.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS

For this previously collected and de-identified secondary use of data, the researchers are not required to report adverse events and no adverse events will be reported to regulatory agencies (GVP Module VIII).

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study will be registered in the EU PAS Register within one month of EMA approval. The protocol will be included within the EU PAS Register. Within one month of study completion and completed review by EMA, a summary of final study results will be uploaded to the EU PAS Register. Additionally, citations for any publications will be added to the data within the EU PAS Register.

A report of the findings of this study will be presented to EMA within two months of finalization of study output from analysts. Additionally, it is intended for the research team to disseminate the research findings widely by publishing the results in a peer-reviewed journal expeditiously to foster greater transparency in clinical research of public health importance. The adopted dissemination approach is also consistent with the transparency principles espoused by the regulatory and learned medical societies in such guidance as EMA GVP (2017), ISPE GPP (2015) and authorship guidelines presented by the International Committee of Medical Journal Editors (ICMJE) recommendations (2019).

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14. Appendix 1. ENCePP Checklist

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Drug Utilisation and Safety Study of Mysimba//Contrave in Europe and the United States

EU PAS Register® number:
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				

1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☒	☐	
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

There is not a date for a progress report; however, an interim report will be done

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	8

Comments:

2.1.4. There are no a priori hypotheses. This is a descriptive study only.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1, 9.2, 9.4, 9.7
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☒	☐	9.7
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	9.7, 11

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Comments:

3.4 This is a descriptive study only. 3.5 This is a database study using deidentified data.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	6, 9.1, 9.4
4.2.2 Age and sex	☐	☒	☐	
4.2.3 Country of origin	☒	☐	☐	9.1, 9.7
4.2.4 Disease/indication	☒	☐	☐	7
4.2.5 Duration of follow-up	☒	☐	☐	9.2-9.7
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.1.1, 9.1.2

Comments:

4.2.2 All uses of Mysimba across all ages and sexes which meet the inclusion criteria in 9.1.1 will be included in the study

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1, 9.3.1.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.4
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.3.1.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.1.1; 9.3.1.2; 9.7.4
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

5.2 Details of data capture reliability in each data source are covered within description of data sources. 5.6 This is not a comparator study, only descriptive.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2, 9.7
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.4
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

6.3 Details of data capture reliability in each data source are covered within description of data sources.

6.4 Study not intended for HTA submission and does not address health economic outcomes

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	

Comments:

7 This is not a comparative study, merely descriptive; however sensitivity analyses are planned

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

8.1 This is not a comparative study

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3.1, 9.4

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3.2, 9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3.3, 9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4, 9.7; SAP (TBD)
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4, 9.7; SAP (TBD)
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4-9.7; SAP (TBD)
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3.1; 9.4, Appendix 2
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.2, 9.7 Appendix 2
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.3.3;9.7, Appendix 2
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☒	☐	

Comments:

9.4 This will be described as part of the SAP, if linkage is necessary for the study

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.6
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.2
10.4 Are stratified analyses included?	☒	☐	☐	9.7
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.5
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7

Comments:

10.5 & 10.6 This is not a comparative study. Sensitivity analyses are planned for misclassification to be detailed in the SAP.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

11.3 This is a database study of deidentified data.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.7; 9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.1, 9.4, 9.7.1

Comments:

12.1.3 This is not a comparative study.

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9.4, 9.8, 11

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: _____

Date: dd/Month/year

Signature: _____

15. Appendix 2. Code lists

Variable	Codes
Mysimba Contrave	ATC: A08AA62 NDC: search terms – Contrave, naltrexone, bupropion
Naltrexone	ATC: N07BB04, A06AH01, N02AA56 NDC: search terms – naltrexone
Bupropion	ATC: N06AX12 NDC: search terms – bupropion
	Concomitant Medications
CYP2B6 inhibitors	See Appendix 2A
CYP2B6 inducers	See Appendix 2A
CYP2B6 substrates	See Appendix 2A
CYP2D6 substrates	See Appendix 2A
Drugs that lower seizure threshold	Propoxyphene, remifentanil, sufentanil, tapentadol, tramadol, baclofen, buspirone, dalfampridine, lithium, mefenamic acid, amphetamine, benzphetamine hydrocholoride, dextroamphetamine, hydroxyamphetamine hydrobromide, lisdexamfetamine dimesylate, methamphetamine hydrochloride, cocaine, phenylpropanolamine, dexamphetamine, methylphenidate
Opioid or opiate agonist	ATC: N02A;
Opium alkaloids & derivatives	ATC: R05DA, N02AA
MAOI	ATC: N04BD, N06AF, N06AG
Seizures	ICD-10: G40
Increase in blood pressure or heart rate	ICD-10: R00.0, R03.0
Hypersensitivity, including Stevens-Johnson	ICD-10: T78, L51
Serotonin syndrome	ICD-10: T43.225A
Suicidality	ICD-10: R45.851, T14.91
Diabetes	ICD-10: E10-E11
Dyslipidaemia	ICD-10: E78
Neuropsychiatric conditions: Mania Bipolar disorder	 ICD-10: F30 ICD-10: F31

Major depressive disorder	ICD-10: F33
Anorexia nervosa	ICD-10: F50.0
Bulimia	ICD-10: F50.2
Hypertension	ICD-10: I10-I16
Uncontrolled hypertension	ICD-10: I10-I16 (with Systolic ≥140 mmHg or diastolic ≥90 mmHg)
Moderate or severe renal impairment	ICD-10: N18.3-N18.5
End stage renal disease	ICD-10: N18.6
Hepatic impairment	ICD-10: K70, K72-K75
Central nervous system tumour	ICD-10: C72
Substance abuse/dependency	ICD-10: F10-F19
Protriptyline*	ATC: N06AA11 NDC: search terms – protriptyline
Benperidol (Anquil)*	ATC: N05AD07 No NDC
Flupentixol (Depixol)*	ATC N05AF01 No NDC
Fluphenazine (Modecate, Prolixin)*	ATC: N05AF02 NDC: search terms – fluphenazine
Levomepromazine (Nozinan)*	ATC: N05AA02 No NDC
Loxapine (Loxitane)*	ATC: N05AH01 NDC: search terms – loxapine
Molindone (Moban)*	ATC: N05AE02 NDC: search terms – molindone
Periciazine*	ATC: N05AC01 No NDC
Sulpiride (Dolmatil, Sulpor)*	ATC: N05AL01 No NDC
Thiothixene (Navane)*	ATC: NONE IDENTIFIED NDC: search terms – thiothixene
Trifluoperazine (Stelazine)*	ATC: N05AB06 NDC: search terms – trifluoperazine
Amisulpride (Solian)	ATC: N05AL05 NDC: search terms – amisulpride
Geodon (ziprasidone)*	ATC: N05AE04 NDC: search terms – ziprasidone

Olanzapine (Zyprexa)	ATC: N05AH03 NDC: search terms – olanzapine
Isocarboxazid (Marplan)*	ATC: N06AF01 NDC: search terms – isocarboxazid
Phenelzine (Nardil)*	ATC: N06AF03 NDC: search terms – phenelzine
Tranylcypromine (Parnate)*	ATC: N06AF04 NDC: search terms – tranylcypromine
Alpelisib	ATC: L01EM03 NDC: search terms – alpelisib
Armodafinil	ATC: N06BA13 NDC: search terms – armodafinil
Atorvastatin	ATC: C10AA05 NDC: search terms – atorvastatin
Avacopan	ATC: NONE IDENTIFIED NDC: search terms – avacopan
Betamethasone	ATC: A07EA04, C05AA05, D07AC01, D07XC01, H02AB01, R01AD06, R03AD04, S01BA06, S01CB04, S02BA07, S03BA03 NDC: search terms – betamethasone
Budesonide	ATC: A07EA06, D07AC09, R01AD05, R03BA02 NDC: search terms – budesonide
Cerivastatin	ATC: C10AA06 No NDC
Dexamethasone	ATC: A01AC02, C05AA09, D07AB19, D07XB05, D10AA03, H02AB02, R01AD03, S01BA01, S01CB01, S02BA06, S03BA01 NDC: search terms – dexamethasone
Fosphenytoin	ATC: N03AB05 NDC: search terms – fosphenytoin
Hydrocortisone	ATC: A01AC03, A07EA02, C05AA01, D07AA02, D07XA01, H02AB09, S01BA02, S01CB03, S02BA01, D07AC16 NDC: search terms – hydrocortisone
Idelalisib	ATC: L01EM01 NDC: search terms – idelalisib
Isavuconazole	ATC: J02AC05 No NDC
Isoflurane	ATC: N01AB06 NDC: search terms – isoflurane
Ivosidenib	ATC: L01XX62 NDC: search terms – ivosidenib
Lemborexant	ATC: N05CM21 NDC: search terms – lemborexant
Lorlatinib	ATC: L01ED05 NDC: search terms – lorlatinib
Lumacaftor	ATC: R07AX30 (with Ivacaftor) NDC: search terms – lumacaftor

Metamizole	ATC: N02BB02 No NDC
Methylprednisolone	ATC: D07AA01, D10AA02, H02AB04, D07AC14 NDC: search terms- methylprednisolone
Midostaurin	ATC: L01EX10 NDC: search terms- rydapt
Mitapivat	ATC: None Identified NDC: search terms- mitapivat
Modafinil	ATC: N06BA07 NDC: search terms- modafinil
Nicardipine	ATC: C08CA04 NDC: search terms- nicardipine
Nilotinib	ATC: L01EA03 NDC: search terms- nilotinib
Olaparib	ATC: L01XK01 NDC: search terms- olaparib
Perampanel	ATC: N03AX22 NDC: search terms- perampanel
Permethrin	ATC: P03AC04, P03AC54 NDC: search terms- permethrin
Pexidartinib	ATC: L01EX15 NDC: search terms- pexidartinib
Phenobarbital	ATC: N03AA02 NDC: search terms- phenobarbital
Pitolisant	ATC: N07XX11 NDC: search terms- pitolisant
Prednisolone	ATC: A07EA01, C05AA04, D07AA03, D07XA02, H02AB06, H02AB06, R01AD02, S01BA04, S01CB02, S02BA03, S03BA02, D07CA03, S01CA02, S02CA01, S03CA02, D07BA01, S01BB02 V03AB05, A01AC54, R01AD52 NDC: search terms- prednisolone
Prednisone	ATC: A07EA03, H02AB07 NDC: search terms- prednisone
Relugolix	ATC: L02BX04, H01CC54 NDC: search terms- relugolix
Rifabutin	ATC: A02BD16, J04AB04 NDC: search terms- rifabutin
Rifampicin	ATC: J04AB02, J04AM02, J04AM07, J04AM05, J04AM06 No NDC
Rifapentine	ATC: J04AB05 NDC: search terms- rifapentine
Rosiglitazone	ATC: 10BD04, A10BD03, A10BG02 No NDC
Sotorasib	ATC: L01XX73

	NDC: search terms- sotorasib
Sulfinpyrazone	ATC: M04AB02 No NDC
Ticagrelor	ATC: B01AC24 NDC: search terms- ticagrelor
Troglitazone	ATC: A10BG01 No NDC
Vemurafenib	ATC: L01EC01 NDC: search terms- vemurafenib
Abametapir	ATC: P03AX07 NDC: search terms- abametapir
Abemaciclib	ATC: L01EF03 NDC: search terms- abemaciclib
Brincidofovir	ATC: J05AB17 No NDC
Cisplatin	ATC: L01XA01 NDC: search terms- cisplatin
Clascoterone	ATC: D10AX06 NDC: search terms- clascoterone
Clotrimazole	ATC: A01AB18, D01AC01, G01AF02 NDC: search terms – clotrimazole
Colchicine	ATC: M04AC01 NDC: search terms- colchicine
Crisaborole	ATC: D11AH06 NDC: search terms- crisaborole
Crizotinib	ATC: L01ED01 NDC: search terms- crizotinib
Curcumin	No ATC NDC: search terms- curcumin
Dabrafenib	ATC: L01EC02 NDC: search terms- dabrafenib
Doxorubicin	ATC: LO1DB01 NDC: search terms- doxorubicin
Dronabinol	ATC: A04AD10 NDC: search terms- dronabinol
Elexacaftor	ATC: R07AX32 NDC: search terms- elexacaftor
Enzalutamide	ATC: L02BB04 NDC: search terms- enzalutamide
Ethanol	ATC: D08AX08, V03AB16, V03AZ01 NDC: search terms- ethanol
Fexinidazole	ATC: P01CA03 NDC: search terms- fexinidazole
Itraconazole	ATC: J02AC02 NDC: search terms- itraconazole

Ketoconazole	ATC: D01AC08, G01AF11, H02CA03, J02AB02 NDC: search terms- ketoconazole
Lenvatinib	ATC: L01EX08 NDC: search terms- lenvatinib
Levoketoconazole	NO ATC NDC: search terms- levoketoconazole
Lopinavir	ATC: J05AR10 NDC: search terms- lopinavir
Manidipine	ATC: C09BB12, C08CA11 No NDC
Memantine	ATC: N06DA53, N06DA53, N06DX01 NDC: search terms- memantine
Menadione	ATC: B02BA02 NDC: search terms- menadione
Methimazole	No ATC NDC: search terms- methimazole
Miconazole	ATC: A01AB09, A07AC01, D01AC02, G01AF04, J02AB01, S02AA13, D01AC52 NDC: search terms- miconazole
Nelfinavir	ATC: J05AE04 NDC: search terms- nelfinavir
Nitric Oxide	ATC: R07AX01 NDC: search terms- nitric oxide
Opicapone	ATC: N04BX04 NDC: search terms- opicapone
Orphenadrine	ATC: N04AB02, M03BC01, M03MC51 NDC: search terms- orphenadrine
Piperaquine	ATC: P01BF07, P01BF05, P01BX02 No NDC
Quazepam	ATC: N05CD10 NDC: search terms- quazepam
Quinidine	ATC: C01BA01, C01BA51, C01BA71 NDC: search terms- quinidine
Raloxifene	ATC: G03XC01 NDC: search terms- raloxifene
Regorafenib	No ATC NDC: search terms- regorafenib
Rifamycin	ATC: A07AA13, D06AX15, J04AB03, S01AA16, S02AA12 NDC: search terms- rifamycin
Rilpivirine	ATC: J05AR21, J05AR19, J05AR08, J05AG05 NDC: search terms- rilpivirine
Roxithromycin	ATC: J01FA06 No NDC
Sorafenib	ATC: L01EX02 NDC: search terms- sorafenib

Sulfaphenazole	ATC: J01ED08 No NDC
Tamoxifen	ATC: L02BA01 NDC: search terms- tamoxifen
Thiotepa	ATC: L01AC01 NDC: search terms- thiotepa
Tirbanibulin	ATC: D06BX03 NDC: search terms- tirbanibulin
Triclabendazole	ATC: P02BX04 NDC: search terms- triclabendazole
Viloxazine	ATC: N06AX09 NDC: search terms- viloxazine
Voriconazole	ATC: J02AC03 NDC: search terms- voriconazole
Abrocitinib	ATC: D11AH08 NDC: search terms- abrocitinib
Amitriptyline	ATC: N06AA09, N06CA01 NDC: search terms- amitriptyline
Amlodipine	ATC: C09XA53, C09AX54, C08CA01, C08CA51, C08GA02, C10BX03, C10BX11, C10BX18, C07FB07, C09DB07, C09DX06, C09DB09, C09DB05, C09DX07, C08CA17, C09BB03, C09DB06, C07FB13, C07FB12, C09DB02, C09DX03, C09BB04, C09BX01, C09BX04, C09BB07, C09BX03, C10BX09, C10BX07, C10BX14, C09DB04, C09DB01, C09DX01 NDC: search terms- amlopidine
Apomorphine	ATC: G04BE07, N04BC07 NDC: search terms- apomorphine
Artemether	ATC: P01BE02, P01BF01 NDC: search terms- artemether
Artemisinin	ATC: P01BE, P01BF, P01BE01, P01BF08, P01BF07 No NDC
Azilsartan	No ATC NDC: search terms- azilsartan
Benzocaine	ATC: C05AD03, D04AB04, N01BA05, R02AD01 NDC: search terms- benzocaine
Benzphetamine	No ATC NDC: search terms- benzphetamine
Brivaracetam	ATC: N03AX23 NDC: search terms- brivaracetam
Brompheniramine	ATC: N06AB01, N06AB51 NDC: search terms- brompheniramine
Cannabidiol	ATC: N03AX24 NDC: search terms- cannabidiol
Carbamazepine	ATC: N03AF01 NDC: search terms- carbamazepine

Cenobamate	ATC: N03AX25 NDC: search terms- cenobamate
Cisapride	ATC: A03FA02 No NDC
Clobazam	ATC: N05BA09 NDC: search terms- clobazam
Clomethiazole	ATC: N05CM02, N05CX04 No NDC
Clopidogrel	ATC: B01AC04 NDC: search terms- clopidogrel
Clotiazepam	ATC: N05BA21 No NDC
Cyclophosphamide	ATC: L01AA01 NDC: search terms- cyclophosphamide
Diazepam	ATC: N05BA01 NDC: search terms- diazepam
Domperidone	ATC: A03FA03 No NDC
Efavirenz	ATC: J05AG03, J05AR06, J05AR11 NDC: search terms- efavirenz
Enasidenib	ATC: L01XX59 NDC: search terms- enasidenib
Epinsathe	No ATC NDC: search terms- epinsathe
Esketamine	ATC: N01AX14, N06AX27 NDC: search terms- esketamine
Estrone	ATC: G03CA07, G03CC04 NDC: search terms- estrone
Flunitrazepam	ATC: N05CD03 No NDC
Halothane	ATC: N01AB01 No NDC
Ifosfamide	ATC: L01AA06 NDC: search terms – ifosfamide
Irinotecan	ATC: L01CE02 NDC: search terms- irinotecan
Ketamine	ATC: N01AX03 NDC: search terms – ketamine
Ketobemidone	ATC: N02AB01, NOAG02 No NDC
Malathion	ATC: P03AX03 NDC: search terms – malathion
Methylphenobarbital	ATC: N03AA01 No NDC
Methyltestosterone	ATC: G03BA02, G03EK01, G03EA01

	NDC: search terms- methyltestosterone
Norgestimate	ATC: G03FA13, G03AA11, G03AB09 NDC: search terms- norgestimate
Ospemifene	ATC: G03XC05 NDC: search terms- ospemifene
Prasugrel	ATC: B01AC22 NDC: search terms- prasugrel
Promethazine	ATC: V03AB05, D04AA10, R06AD02, R06AD52 NDC: search terms- promethazine
Propofol	ATC: N01AX10 NDC: search terms- propofol
Romidepsin	ATC: L01XH02 NDC: search terms- romidepsin
Ropivacaine	ATC: N01BB09 NDC: search terms- ropivacaine
Seratrodast	ATC: R03DX06 No NDC
Sevoflurane	ATC: N01AB08 NDC: search terms- sevoflurane
Temazepam	ATC: N05CD07 NDC: search terms- temazepam
Testosterone	ATC: G03BA03, G03EA02 NDC: search terms- testosterone
Tretinoin	ATC: D10AD01, L01XF01, D10AD51 NDC: search terms- tretinoin
Trifarotene	ATC: D10AD06 NDC: search terms- trifarotene
Valproic acid	ATC: N03AG01 NDC: search terms- valproic acid
Velpatasvir	ATC: J05AP55, J05AP56 NDC: search terms- velpatasvir
Verapamil	ATC: C09BB10, C08DA01, C08DA51 NDC: search terms- verapamil
Voxelotor	ATC: B06AX03 NDC: search terms- voxelotor
Zanubrutinib	ATC: L01EL03 NDC: search terms- zanubrutinib
Acebutolol	ATC: C07AB04, C07BB04 NDC: search terms- acebutolol
Acetaminophen	No ATC NDC: search terms- acetaminophen
Almotriptan	ATC: N02CC05 NDC: search terms- almotriptan
Alogliptin	ATC: A10BH04, A10BD13, A10BD09 NDC: search terms- alogliptin

Alprenolol	ATC: C07AA01 No NDC
Aminophenazone	ATC: N02BB03, N02BB53, N02BB73 No NDC
Amoxapine	ATC: N06AA17 NDC: search terms- amoxapine
Amphetamine	No ATC NDC: search terms- amphetamine
Amprenavir	ATC: J05AE05 No NDC
Aprindine	ATC: C01BB04 No NDC
Arformoterol	No ATC NDC: search terms- arformoterol
Aripiprazole	ATC: N05AX12 NDC: search terms- aripiprazole
Asenapine	ATC: N05AH05 NDC: search terms- asenapine
Astemizole	ATC: R06AX11 No NDC
Asunaprevir	ATC: J05AP06, J05AP58 No NDC
Atenolol	ATC: C07AB03, C07FB03, C07CB53, C07BB03, C07DB01 NDC: search terms- atenolol
Atomoxetine	ATC: N06BA09 NDC: search terms- atomoxetine
Azelastine	ATC: R01AC03, R06AX19, S01GX07 NDC: search terms- azelastine
Befunolol	ATC: S01ED06 No NDC
Belumosudil	ATC: L04AA48 NDC: search terms- belumosudil
Benzatropine	ATC: N04AC01 No NDC
Benzyl alcohol	ATC: P03AX06 NDC: search terms- benzyl alcohol
Bepridil	ATC: C08EA02 No NDC
Betaxolol	ATC: C07AB05, S01ED02, S01ED52 NDC: search terms- betaxolol
Bevantolol	ATC: C07AB06, C07BB06 No NDC
Bopindolol	ATC: C07AA17, C07CA17 No NDC
Bortezomib	ATC: L01XG01

	NDC: search terms- bortezomib
Brexpiprazole	ATC: N05AX16 NDC: search terms- brexpiprazole
Bupivacaine	ATC: N01BB01, N01BB59, N01BB51 NDC: search terms- bupivacaine
Bupranolol	ATC: C07AA10 No NDC
Buspirone	ATC: N05BE01 NDC: search terms – buspirone
Caffeine	ATC: D11AX26, N06BC01, V04CG03 NDC: search terms – caffeine
Cariprazine	ATC: N05AX15 NDC: search terms – cariprazine
Carteolol	ATC: C07AA15, S01ED05, S01ED55 NDC: search terms – carteolol
Carvedilol	ATC: C07AG02, C07FX06 NDC: search terms- carvedilol
Celecoxib	ATC: C08CA51, L01XX33, M01AH01, N02AJ16 NDC: search terms- celecoxib
Celiprolol	ATC: C07AB08 No NDC
Cevimeline	ATC: N07AX03 NDC: search terms- cevimeline
Chloroquine	ATC: P01BA01, P01BB52 NDC: search terms- chloroquine
Chlorpheniramine	No ATC NDC: search terms- chlorpheniramine
Chlorpromazine	ATC: N05AA01 NDC: search terms- chlorpromazine
Chlorzoxazone	ATC: M03BB03, M03BB53, M03BB73 NDC: search terms- chlorzoxazone
Ciclesonide	ATC: R01AD13, R03BA08 NDC: search terms- ciclesonide
Cilostazol	ATC: B01AC23 NDC: search terms- cilostazol
Cinnarizine	ATC: N07CA02, N07CA52 No NDC
Citalopram	ATC: N06AB04 NDC: search terms- citalopram
Clevidipine	ATC: C08CA16 NDC: search terms- clevidipine
Clomipramine	ATC: N06AA04 NDC: search terms- clomipramine
Clonidine	ATC: C02AC01, N02CX02, S01EA04, C02LC01, C02LC51 NDC: search terms-clonidine (exclude apraclonidine)

Cloranolol	ATC: C07AA27 No NDC
Clozapine	ATC: N05AH02 NDC: search terms- clozapine
Codeine	ATC: R05DA04, N02AJ07, N02AJ08, N02AJ09, N02AJ06, N02AA59, N02AA79 NDC: search terms- codeine
Cyclobenzaprine	ATC: M03BX08 NDC: search terms- cyclobenzaprine
Dacomitinib	ATC: L01EB07 NDC: search terms- dacomitinib
Dapagliflozin	ATC: A10BK01, A10BD15, A10BD25, A10BD21 NDC: search terms- dapagliflozin
Dapoxetine	ATC: G04BX14 No NDC
Darifenacin	ATC: G04BD10 NDC: search terms- darifenacin
Dasabuvir	ATC: J05AP09, J05AP52 NDC: search terms- dasabuvir
Debrisoquine	ATC: C02CC04 NDC: search terms- debrisoquine
Delavirdine	ATC: J05AG02 No NDC
Desipramine	ATC: N06AA01 NDC: search terms- desipramine
Deutetrabenazine	ATC: N07XX16 NDC: search terms- deutetrabenazine
Dexchlorpheniramine	ATC: R06AB02, R06AB52 NDC: search terms- dexchlorpheniramine
Dexfenfluramine	ATC: A08AA04 No NDC
Dextroamphetamine	No ATC NDC: search terms- dextroamphetamine
Dextromethorphan	ATC: R05DA09, N07XX59 NDC: search terms- dextromethorphan
Dextropropoxyphene	ATC: N02AC04, N02AC54, N02AC74 No NDC
Dihydrocodeine	ATC: N02AA08, N02AJ02, N02AJ03, N02AJ01, N02AA58 NDC: search terms- dihydrocodeine
Diltiazem	ATC: C05AE03, C08DB01 NDC: search terms- diltiazem
Diphenhydramine	ATC: D04AA32, R06AA02, D04AA33, R06AA52 NDC: search terms- diphenhydramine
Dolasetron	ATC: A04AA04 NDC: search terms- dolasetron

Donepezil	ATC: N06DA02, N06DA52, N06DA53 NDC: search terms- donepezil
Dosulepin	ATC: N06AA16 No NDC
Doxazosin	ATC: C02CA04 NDC: search terms- doxazosin
Doxepin	ATC: D04AX01, N06AA12 NDC: search terms- doxepin
Dronedarone	ATC: C01BD07 NDC: search terms- dronedarone
Duloxetine	ATC: N06AX21 NDC: search terms- duloxetine
Elagolix	ATC: H01CC03 NDC: search terms- elagolix
Eletriptan	ATC: N02CC06 NDC: search terms- eletriptan
Eliglustat	ATC: A16AX10 NDC: search terms- eliglustat
Encainide	ATC: C01BC08 No NDC
Encorafenib	ATC: L01EC03 NDC: search terms- encorafenib
Epanolol	ATC: C07AB10 No NDC
Epinastine	ATC: R06AX24, S01GX10 NDC: search terms- epinastine
Erlotinib	ATC: L01EB02 NDC: search terms- erlotinib
Escitalopram	ATC: N06AB10 NDC: search terms- escitalopram
Esmolol	ATC: C07AB09 NDC: search terms- esmolol
Ethylmorphine	ATC: R05DA01, S01XA06 No NDC
Fenfluramine	ATC: A08AA02, N03AX26 NDC: search terms- fenfluramine
Fesoterodine	ATC: G04BD11 NDC: search terms- fesoterodine
Flecainide	ATC: C01BC04 NDC: search terms- flecainide
Flunarizine	ATC: N07CA03 No NDC
Fluoxetine	ATC: N06AB03, N06CA03 NDC: search terms- fluoxetine
Fluvastatin	ATC: C10AA04

	NDC: search terms- fluvastatin
Fluvoxamine	ATC: N06AB08 NDC: search terms- fluvoxamine
Formoterol	ATC: R03AC13, R03CC15, R03AL05, R03AK08, R03AK07, R03AK11, R03AL07, R03AK09, R03AL10, R03AL09, R03AL11 NDC: search terms- formoterol
Fusidic acid (Fucidin)	ATC: D06AX01, D09AA02, J01XC01, S01AA13 NDC: search terms- fucidin
Galantamine	ATC: N06DA04 NDC: search terms- galantamine
Gefitinib	ATC: L01EB01 NDC: search terms- gefitinib
Glycopyrronium	ATC: R03AL07, R03AL09, R03AL11, D11AA01, A03AB02, R03BB06, A03CA05, R03AL04, R03AL12 NDC: search terms- glycopurronium
Haloperidol	ATC: N05AD01 NDC: search terms- haloperidol
Hydroxychloroquine	ATC: P01BA02 NDC: search terms- hydrochloroquine
Ibrutinib	ATC: L01EL01 NDC: search terms- ibrutinib
Idarubicin	ATC: L01DB06 NDC: search terms- idarubicin
Iloperidone	ATC: N05AX14 NDC: search terms- iloperidone
Imatinib	ATC: L01EA01 NDC: search terms- imatinib
Imipramine	ATC: N06AA02, N06AA03 NDC: search terms- imipramine
Indenolol	No ATC NDC: search terms- indenolol
Ipecac	No ATC NDC: search terms- ipecac
Istradefylline	ATC: N04CX01 NDC: search terms- istradefylline
Ivermectin	ATC: D11AX22, P02CF01 NDC: search terms- ivermectin
Ixazomib	ATC: L01XG03 NDC: search terms- ixazomib
Labetalol	ATC: C07AG01, C07CG01, C07BG01 NDC: search terms- labetalol
Landiolol	ATC: C07AB14 No NDC
Letermovir	ATC: J05AX18 NDC: search terms- letermovir

Levobunolol	ATC: S01ED03 NDC: search terms- levobunolol
Levomilnacipran	ATC: N06AX28 NDC: search terms- levomilnacipran
Lidocaine	ATC: C01BB01, C05AD01, D04AB01, N01BB02, R02AD02, S01HA07, S02DA01, N01BB52 NDC: search terms- lidocaine
Lisdexamfetamine	ATC: N06BA12 NDC: search terms- lisdexamfetamine
Lisuride	ATC: G02CB02, N02CA07 No NDC
Lofexidine	ATC: N07BC04 NDC: search terms- lofexidine
Loperamide	ATC: A07DA03, A07DA05, A07DA53 NDC: search terms- loperamide
Loratadine	ATC: R06AX13 NDC: search terms- loratadine
Lorcaserin	ATC: A08AA11 NDC: search terms- lorcaserin
Lorpiprazole	ATC: A07DA03, A07DA03, A07DA53 No NDC
Maprotiline	ATC: N06AA21 No NDC
Meclizine	No ATC NDC: search terms- meclizine
Meperidine	No ATC NDC: search terms- meperidine
Mephenytoin	ATC: N03AB04, N03AB54 No NDC
Mepindolol	ATC: C07AA14 No NDC
Mequitazine	ATC: R06AD07 No NDC
Mesoridazine	ATC: N05AC03 No NDC
Metamfetamine	ATC: N06BA03 No NDC
Methoxyflurane	ATC: N02BG09 No NDC
Methylene blue	No ATC NDC: search terms- methylene blue
Metipranolol	ATC: S01ED04, C07BA68, S01ED54 No NDC
Metoclopramide	ATC: A03FA01 NDC: search terms- metoclopramide

Metoprolol	ATC: C07AB02, C07FX03, C07FB13, C07FB02, C07FX05, C07CB02, C07BB02, C07BB52 NDC: search terms- metoprolol
Mexiletine	ATC: C01BB02 NDC: search terms- mexiletine
Mianserin	ATC: N06AX03 No NDC
Midodrine	ATC: C01CA17 NDC: search terms- midodrine
Minaprine	ATC: N06AX07 No NDC
Mirabegron	ATC: G04BD12 NDC: search terms- mirabegron
Mirtazapine	ATC: N06AX11 NDC: search terms- mirtazapine
Moclobemide	ATC: N06AG02 No NDC
Nadolol	ATC: C07AA12, C07BA12 NDC: search terms- nadolol
Nateglinide	ATC: A10BX03 NDC: search terms- nateglinide
Nebivolol	ATC: C07AB12, C07FB12, C07BB12, C09DX05 NDC: search terms- nebivolol
Nefazodone	ATC: N06AX06 No NDC
Netupitant	No ATC NDC: search terms- netupitant
Nevirapine	ATC: J05AG01, J05AR07, J05AR05 NDC: search terms- nevirapine
Nicergoline	ATC: C04AE02 No NDC
Nicotine	ATC: N07BA, N07BA01 NDC: search terms- nicotine
Nifedipine	ATC: C07FB03, C08CA05, C08GA01, C08CA55 NDC: search terms- nifedipine
Nortriptyline	ATC: N06AA10 NDC: search terms- nortiptyline
Olanzapine	ATC: N05AH03 NDC: search terms- olanzapine
Oliceridine	ATC: N02AX07 NDC: search terms- oliceridine
Ondansetron	ATC: A04AA01 NDC: search terms- ondansetron
Osilodrostat	ATC: H02CA02 NDC: search terms- osilodrostat

Oxamniquine	ATC: P02BA02 No NDC
Oxprenolol	ATC: C07AA02, C07AC02, C07BA02 No NDC
Paliperidone	ATC: N05AX13 NDC: search terms- paliperidone
Palonosetron	ATC: A04AA05, A04AA55 NDC: search terms- palonosetron
Paroxetine	ATC: N06AB05 NDC: search terms- paroxetine
Pazopanib	ATC: L01EX03 NDC: search terms- pazopanib
Penbutolol	ATC: C07AA23, C07CA23 No NDC
Pentamidine	ATC: P01CX01 NDC: search terms- pentamidine
Perhexiline	ATC: C08EX02 No NDC
Perphenazine	ATC: N05AB03 No NDC
Phenacetin	ATC: N02BE03, N02BE73 NDC: search terms- phenacetin
Phenformin	ATC: A10BA01, A10BD01 No NDC
Phenytoin	ATC: N03AB04, N03AB52 NDC: search terms- phenytoin
Pimavanserin	ATC: N05AX17 NDC: search terms- pimavanserin
Pimozide	ATC: N05AG02 NDC: search terms- pimozide
Pindolol	ATC: C07AA03 NDC: search terms- pindolol
Piperazine	ATC: P02CB01 NDC: search terms- piperazine
Pipotiazine	ATC: N05AC04 No NDC
Pirfenidone	ATC: L04AX05 NDC: search terms- pirfenidone
Ponatinib	ATC: L01EA05 NDC: search terms- ponatinib
Practolol	ATC: C07AB01 No NDC
Pralsetinib	ATC: L01EX23 NDC: search terms- pralsetinib
Procainamide	ATC: C01BA02

	NDC: search terms- procainamide
Prochlorperazine	ATC: N05AB04 NDC: search terms- prochlorperazine
Progesterone	ATC: G03DA04, G03FA04 NDC: search terms- progesterone
Promazine	ATC: N05AA03 NDC: search terms- promazine
Propacetamol	ATC: N02BE05 No NDC
Propafenone	ATC: C01BC03 NDC: search terms- propafenone
Propranolol	ATC: C07AA05, C07FX01, C07BA05 NDC: search terms- propranolol
Quetiapine	ATC: N05AH04 NDC: search terms- quetiapine
Quinine	ATC: M09AA, P01BC01, M09AA72 NDC: search terms- quinine
Ranolazine	ATC: C01EB18 NDC: search terms- ranolazine
Remdesivir	ATC: J05AB16 NDC: search terms- remdesivir
Remoxipride	ATC: N05AL04 No NDC
Revefenacin	ATC: R03BB08 NDC: search terms- revefenacin
Ripretinib	ATC: L01EX19 NDC: search terms- ripretinib
Risperidone	ATC: N05AX08 NDC: search terms- risperidone
Ritonavir	ATC: J05AR23, J05AR26, J05AP52, J05AR10, J05AP53, J05AE03 NDC: search terms- ritonavir
Rotigotine	ATC: N04BC09 NDC: search terms- rotigotine
Rucaparib	ATC: L01XK03 NDC: search terms- rucaparib
Rupatadine	ATC: R06AX28 No NDC
Selegiline	ATC: N04BD01 NDC: search terms- selegiline
Sertindole	ATC: N05AE03 No NDC
Sertraline	ATC: N06AB06 NDC: search terms- sertraline
Sildenafil	ATC: G04BE03 NDC: search terms- sildenafil

Simvastatin	ATC: C10AA01, C10BX01, C10BA02, C10BA04, C10BX04, A10BH51 NDC: search terms- simvastatin
Solifenacin	ATC: G04BD08, G04CA53 NDA: search terms- solifenacin
Sotalol	ATC: C07AA07, C07FX02, C07BA07 NDA: search terms- sotalol
Sparteine	ATC: C01BA04 No NDC
Tafenoquine	ATC: P01BA07 NDC: search terms- tafenoquine
Talinolol	ATC: C07AB13 No NDC
Tamsulosin	ATC: G04CA02, G04CA52, C04CA53, G04CA54 NDC: search terms- tamulosin
Tapentadol	ATC: N02AX06 NDC: search terms- tapentadol
Tegaserod	ATC: A06AX06 No NDC
Terfenadine	ATC: R06AX12 No NDC
Tertatolol	ATC: C07AA16 No NDC
Tetrabenazine	ATC: N07XX16, N07XX06 NDC: search terms- tetrabenazine
Theophylline	ATC: R03DA02, R03DA12, R03DA04, R03DB04, R03DA54, R03DA74 NDC: search terms- theophylline
Thioridazine	ATC: N05AC02 NDC: search terms- thioridazine
Ticlopidine	ATC: B01AC05 No NDC
Timolol	ATC: C07AA06, S01ED01, C07BA06, S01ED51, C07DA06 NDC: search terms- timolol
Tiotropium	ATC: R03AL10, R03AL06, R03BB04, R03BB54 NDC: search terms- tiotropium
Tipranavir	ATC: J05AE09 NDC: search terms – tipranavir
Tolterodine	ATC: G04BD07 NDC: search terms – tolterodine
Trabectedin	ATC: L01CX01 NDC: search terms – trabectedin
Trazodone	ATC: N06AX05 NDC: search terms- trazodone
Trimipramine	ATC: N06AA06

	NDC: search terms- trimipramine
Umifenovir	ATC: J05AX13 No NDC
Upadacitinib	ATC: L04AA44 NDC: search terms- upadacitinib
Valbenazine	ATC: N07XX13 NDC: search terms- valbenazine
Venlafaxine	ATC: N06AX23, N06AX16 NDC: search terms- venlafaxine
Vernakalant	ATC: C01BG11 No NDC
Vilazodone	ATC: N06AX24 NDC: search terms – vilazodone
Vortioxetine	ATC: N06AX26 NDC: search terms – vortioxetine
Yohimbine	ATC: G04BE04 No NDC
Zolpidem	ATC: N05CF02 NDC: search terms – zolpidem
Zuclopenthixol (Clopixol, Clopixol Acuphase, Clopixol Concentrate)	ATC: N05AF05 No NDC
Buprenorphine	ATC: N02AE01, N07BC01, N07BC51 NDC: search terms – buprenorphine
Hydrocodone	ATC: R05DA03 NDC: search terms – hydrocodone
Methadone	ATC: N07BC05, N07BC02, N02AC52, R05DA06 NDC: search terms – methadone
Morphine*	ATC: N07BC06, R05DA01, S01XA06, N02AA01, N02AG01, A07DA52, N02AA51, N02AA04, R05DA05 NDC: search terms – morphine sulphate
Opium	ATC: N02AA, R05DA, R05FA, A07DA02, N02AA02, R05DA05, R05FA02, R05FA01 NDC: search terms – belladonna and opium
Oxycodone	ATC: N02AA05, N02AJ17, N02AJ18, N02AJ19, N02AA55, N02AA56 NDC: search terms – oxycodone
Oxymorphone	ATC: N02AA11 NDC: search terms – oxymorphone
Tramadol	ATC: N02AX02, N02AJ13, N02AJ14, N02AJ15, N02AJ16 NDC: search terms – tramadol

16. Appendix 2a

CYP2B6 inhibitors	CYP2B6 inducers	CYP2B6 substrates	CYP2D6
Abametapir	Cenobamate	Cenobamate	4-Methoxyamphetamine
Abemaciclib	Clotrimazole	Enasidenib	5-methoxy-N,N-dimethyltryptamine
Amlodipine	Dabrafenib	Fexinidazole	
Amprenavir	Enasidenib	Medical Cannabis	Acebutolol
Azelastine	Fexinidazole	Artemether	Acetaminophen
Brincidofovir	Medical Cannabis	Artemisinin	Almotriptan
Cannabidiol	Pexidartinib	Carbamazepine	Alogliptin
Cannabinol	Rifamycin	Cyclophosphamide	Alprenolol
Cenobamate	Ritonavir	Efavirenz	Aminophenazone
Cisplatin	Simvastatin	Esketamine	Amitriptyline
Clascoterone	Sorafenib	Isoflurane	Amoxapine
Clopidogrel	Alpelisib	Methadone	Amphetamine
Clotrimazole	Armodafinil	Nevirapine	Amprenavir
Colchicine	Artemether	Perampanel	Anisodamine
Crisaborole	Artemisinin	Permethrin	Antipyrine
Crizotinib	Atorvastatin	Phenytoin	Aprindine
Curcumin	Avacopan	Thalidomide	Arformoterol
Curcumin sulfate	Betamethasone	Zanubrutinib	Aripiprazole
Dabrafenib	Budesonide	Amlodipine	Aripiprazole lauroxil
Desipramine	Carbamazepine	Cannabidiol	Arotinolol
Doxorubicin	Cerivastatin	Clopidogrel	Asenapine
Dronabinol	Cyclophosphamide	Selegiline	Astemizole
Duloxetine	Dexamethasone	Sertraline	Asunaprevir
Elexacaftor	Dexamethasone acetate	Tamoxifen	Atenolol
Enasidenib	Efavirenz	Abrocitinib	Atomoxetine
Enzalutamide	Esketamine	Amitriptyline	Azelastine
Ethanol	Fluvastatin	Antipyrine	Azimilide
Fexinidazole	Fosphenytoin	Apomorphine	Befunolol
Fluvoxamine	Hydrocortisone	Asunaprevir	Belumosudil
Itraconazole	Idelalisib	Azilsartan medoxomil	Benzatropine
Ketoconazole	Isavuconazole	Banoxantrone	Benzocaine
Lenvatinib	Isoflurane	Benzocaine	Benzyl alcohol
Levoketoconazole	Ivosidenib	Benzphetamine	Bepridil
Lopinavir	Lemborexant	Brivaracetam	Betaxolol
Manidipine	Letermovir	Brompheniramine	Bevantolol
Medical Cannabis	Lorlatinib	Bupropion	Bicifadine
Memantine	Lumacaftor	Cinnarizine	Bopindolol
Menadione	Mavacamten	Cisapride	Bortezomib
Methimazole	Metamizole	Clobazam	Brexpiprazole
Methylene blue	Methadone	Clomethiazole	Bucindolol
Miconazole	Methylprednisolone	Clotiazepam	Bufuralol
Modafinil	Midostaurin	Coumarin	Bupivacaine
Nelfinavir	Mitapivat	Dexloxiglumide	Bupranolol
Nitric Oxide	Modafinil	Dextromethorphan	Buprenorphine
Opicapone	Nevirapine	Diazepam	Buspirone
Orphenadrine	Nicardipine	Diclofenac	Butyrfentanyl
Paroxetine	Nifedipine	Domperidone	Caffeine
Pexidartinib	Nilotinib	Dosulepin	Cannabidiol
Phencyclidine	Olaparib	Epinastine	Cariprazine
Piperaquine	Perampanel	Estrone	Carteolol
Quazepam	Permethrin	Ethylmorphine	Carvedilol
Quinidine	Phenobarbital	Fenfluramine	Celecoxib

Raloxifene	Phenytoin	Flunitrazepam	Celiprolol
Regorafenib	Pitolisant	Fluoxetine	Cevimeline
Rifamycin	Prednisolone phosphate	Ganaxolone	Chloroquine
Rilpivirine	Prednisone	Glycopyrronium	Chlorpheniramine
Ritonavir	Relugolix	Halothane	Chlorpromazine
Roxithromycin	Rifabutin	Hydrocodone	Chlorzoxazone
Selegiline	Rifampicin	Ifosfamide	Ciclesonide
Sertraline	Rifampin	Ifosfamide	Cilostazol
Simvastatin	Rifapentine	Imipramine	Cinnarizine
Sorafenib	Rosiglitazone	Irinotecan	Citalopram
Sulfaphenazole	Sulfinpyrazone	Istradefylline	Clevidipine
Tamoxifen	Tecovirimat	Ixazomib	Clomipramine
Thiotepa	Thalidomide	Ketamine	Clonidine
Ticlopidine	Ticagrelor	Ketobemidone	Cloranolol
Tirbanibulin	Troglitazone	Kitamine	Clozapine
Triclabendazole	Vemurafenib	Lidocaine	Codeine
Viloxazine	Zanubrutinib	Loperamide	Cyclobenzaprine
Voriconazole		Loratadine	Dacomitinib
		Lorcaserin	Dapagliflozin
		Malathion	Dapoxetine
		Meperidine	Darifenacin
		Mephenytoin	Dasabuvir
		Methoxyflurane	Debrisoquine
		Methylphenobarbital	Delavirdine
		Methyltestosterone	Desipramine
		Mexiletine	Deutetrabenazine
		Mianserin	Dexchlorpheniramine
		Nicotine	Dexchlorpheniramine maleate
		Norgestimate	Dexfenfluramine
		Osilodrostat	Dextroamphetamine
		Ospemifene	Dextromethorphan
		Ospemifene	Dextropropoxyphene
		Perhexiline	Dihydrocodeine
		Prasugrel	Diltiazem
		Promethazine	Diphenhydramine
		Propofol	Dolasetron
		Romidepsin	Domperidone
		Ropivacaine	Donepezil
		Seratrodast	Dosulepin
		Sevoflurane	Doxazosin
		Temazepam	Doxepin
		Testosterone	Dronedarone
		Testosterone cypionate	Duloxetine
		Testosterone enanthate	Elagolix
		Testosterone undecanoate	Eletriptan
		Tramadol	Eliglustat
		Tretinoin	Enasidenib
		Trifarotene	Encainide
		Valproic acid	Enclomiphene
		Velpatasvir	Encorafenib
		Verapamil	Epanolol
		Vortioxetine	Epinastine
		Voxelotor	Erlotinib
			Esatenolol
			Escitalopram
			Esmirtazapine
			Esmolol
			Ethylmorphine

			Fenfluramine Fesoterodine Fexinidazole Flecainide Flunarizine Fluoxetine Fluvastatin Fluvoxamine Formoterol Fusidic acid Galantamine Ganaxolone Gefitinib Glycopyrronium Haloperidol Hydrocodone Hydroxychloroquine Ibrutinib Idarubicin Iloperidone Imatinib Imipramine Indenolol Ipecac Istradefylline Ivermectin Ixazomib Labetalol Landiolol Letermovir Levobetaxolol Levobunolol Levomilnacipran Lidocaine Lisdexamfetamine Lisuride Lofexidine Loperamide Lopinavir Loratadine Lorcaserin Lorpiprazole Lysergic acid diethylamide Maprotiline Meclizine Medical Cannabis Meperidine Mephenytoin Mepindolol Mequitazine Mesoridazine Metamfetamine Methadone Methotrimeprazine Methoxyflurane Methylene blue Metipranolol Metoclopramide

			Metoprolol Mexiletine Mianserin Midodrine Midomafetamine Minaprine Mirabegron Mirtazapine Moclobemide Nabiximols Nadolol Nateglinide Nebivolol Nefazodone Netupitant Nevirapine Nicergoline Nicotine Nifedipine Nortriptyline Olanzapine Oliceridine Ondansetron Opium Osilodrostat Oxamniquine Oxprenolol Oxycodone Oxymorphone Paliperidone Palonosetron Paroxetine Pazopanib Penbutolol Pentamidine Perhexiline Perospirone Perphenazine Phenacetin Phenformin Phenytoin Pimavanserin Pimozide Pindolol Piperazine Pipotiazine Pirfenidone Pitolisant Ponatinib Practolol Pralsetinib Procainamide Prochlorperazine Progesterone Promazine Promethazine Propacetamol Propafenone

			Propranolol Quetiapine Quinine Ranolazine Remdesivir Remoxipride Repinotan Revefenacin Ripretinib Risperidone Ritonavir Rotigotine Rucaparib Rupatadine Selegiline Sertindole Sertraline Sildenafil Simvastatin Solifenacin Sotalol Sparteine Tafenoquine Talinolol Tamoxifen Tamsulosin Tapentadol Tapinarof Tegaserod Terfenadine Tertatolol Tesmilifene Tetrabenazine Theophylline Thioridazine Ticlopidine Timolol Tiotropium Tipranavir Tolterodine Trabectedin Tramadol Trazodone Triclabendazole Trimipramine Umeclidinium Umifenovir Upadacitinib Valbenazine Venlafaxine Vernakalant Vilazodone Viloxazine Vortioxetine Yohimbine Zolpidem Zuclopenthixol

Opioids
Acetaminophen/Caffeine/Dihydrocodeine bitartrate
Acetaminophen/Codeine Phosphate
Acetaminophen/Oxycodone Hydrochloride
alfentanil
Alfentanil Hydrochloride
Aspirin/Caffeine/Dihydrocodeine Bitartrate
Aspirin/Codeine Phosphate
Aspirin/Oxycodone Hydrochloride
Belladonna/Opium
Benzhydrocodone/Acetaminophen
bezitramide
Buprenorphine
Buprenorphine Hydrochloride
Buprenorphine/Naloxone
Butalbital/Acetaminophen/Caffeine/Codeine Phosphate
Butalbital/Aspirin/Caffeine/Codeine Phosphate
Butorphanol Tartrate
butorphanol
Carisoprodol/Aspirin/Codeine Phosphate
Celecoxib/Tramadol Hydrochloride
Chlorpheniramine Polistirex/Codeine Polistirex
codeine
codeine and acetylsalicylic acid
codeine and ibuprofen
codeine and other non-opioid analgesics
codeine and paracetamol
Codeine Phosphate/Guaifenesin
Codeine Sulfate
codeine, combinations excl. psycholeptics
codeine, combinations with psycholeptics
dextromoramide
dextropropoxyphene
dextropropoxyphene, combinations excl. psycholeptics
dextropropoxyphene, combinations with psycholeptics
dezocine
Difelikefalin
Difenoxin Hydrochloride/Atropine Sulfate
dihydrocodeine and acetylsalicylic acid
dihydrocodeine and other non-opioid analgesics
dihydrocodeine and paracetamol
dihydrocodeine
dihydrocodeine, combinations
Diphenoxylate Hydrochloride/Atropine Sulfate
Fentanyl Citrate
fentanyl
FENTANYL/DROPERIDOL
hydrocodone
Hydrocodone Bitartrate
Hydrocodone Bitartrate/Acetaminophen
Hydrocodone Bitartrate/Chlorpheniramine Maleate
Hydrocodone bitartrate/Guaifenesin
Hydrocodone Bitartrate/Homatropine Methylbromide
Hydrocodone Bitartrate/Ibuprofen
Hydrocodone bitartrate/Pseudoephedrine Hydrochloride
Hydrocodone Polistirex/Chlorpheniramine Polistirex
Hydrocodone/Chlorpheniramine/Pseudoephedrine
Hydrocodone/Pseudoephedrine/Guaifenesin

hydromorphone
hydromorphone and antispasmodics
hydromorphone and naloxone
Hydromorphone Hydrochloride
hydromorphone
ketobemidone and antispasmodics
ketobemidone
LEVOMETHADYL
LEVORPHANOL
Levorphanol Tartrate
meperidine
Meperidine Hydrochloride
Meperidine Hydrochloride/Promethazine Hydrochloride
meptazinol
methadone
Methadone Hydrochloride
methadone, combinations excl. psycholeptics
morphine and antispasmodics
Morphine Sulfate
Morphine Sulfate Liposome
Morphine Sulfate/Naltrexone Hydrochloride
morphine
morphine, combinations
Nalbuphine Hydrochloride
nalbuphine
nicomorphine
oliceridine
opium
oxycodone and acetylsalicylic acid
oxycodone and ibuprofen
oxycodone and naloxone
oxycodone and naltrexone
oxycodone and paracetamol
Oxycodone Hydrochloride
Oxycodone Hydrochloride/Naloxone Hydrochloride
Oxycodone Hydrochloride/Naltrexone Hydrochloride
oxycodone
Oxycodone/Ibuprofen
Oxymorphone Hydrochloride
oxymorphone
papaveretum
Paregoric
pentazocine
pethidine and antispasmodics
pethidine
pethidine, combinations excl. psycholeptics
pethidine, combinations with psycholeptics
phenazocine
piritramide
Promethazine Hydrochloride/Codeine Phosphate
Promethazine/Phenylephrine/Codeine Phosphate
PROPOXYPHENE
PROPOXYPHENE NAPSYLATE/ACETAMINOPHEN
remifentanil
Remifentanil Hydrochloride
sufentanil
Sufentanil Citrate
Tapentadol Hydrochloride

tapentadol
tilidine and naloxone
tilidine
tramadol and celecoxib
tramadol and dexketoprofen
tramadol and other non-opioid analgesics
tramadol and paracetamol
Tramadol Hydrochloride
Tramadol Hydrochloride/Acetaminophen
tramadol
Triprolidine/Pseudoephedrine/Codeine

Opium alkaloid and derivatives

ATC: R05A

acetyldihydrocodeine
codeine
combinations
dextromethorphan
dimemorfan
ethylmorphine
hydrocodone
normethadone
noscapine
opium alkaloids with morphine
pholcodine
thebacon

Appendix 3. Variable Availability by Country (final list to be confirmed in SAP)

LEGEND: "--" indicates that the information is not available
Partial = may be available for some patients
Limited = anticipated to be underreported
Yes = likely to be available if true for patient
Unlikely = available for some patients; may not be accurate
Calculated = assumptions can be used to derive a variable for this information

Variable	US	Denmark	Norway	Sweden	Finland
Mysimba prescription	Yes	--	--	--	--
Date of Mysimba prescription	Yes	--	--	--	--
Mysimba dispensing	Partial	Yes	Yes	Yes	Yes
Date of Mysimba dispensing	Partial	Yes	Yes	Yes	Yes
Mysimba dosage for each dispensing	Partial	--	--	--	--
Initial titration scheme	Maybe	--	--	--	--
Dosing of Mysimba during titration	Maybe	--	--	--	--
Dose adjustment of Mysimba (e.g., for special population)	Partial	--	--	--	--
Maintenance dose of Mysimba	Maybe	--	--	--	--
Mysimba days' supply	Calculated	Calculated	Calculated	Calculated	Calculated
Date of eligibility/enrolment available to identify continued engagement/recording of clinic visits	Partial	Yes	Yes	Yes	Yes
Age	Yes	Yes	Yes	Yes	Yes
Sex	Yes	Yes	Yes	Yes	Yes
BMI	Partial	--	--	--	--
Height	Partial	--	--	--	--
Weight	Partial	--	--	--	--
Diabetes	Yes	Yes	Yes	Yes	Yes
Dyslipidaemia	Yes	Yes	Yes	Yes	Yes

Anorexia nervosa	Yes	Yes	Yes	Yes	Yes
Bulimia	Yes	Yes	Yes	Yes	Yes
Hypertension	Yes	Yes	Yes	Yes	Yes
Uncontrolled hypertension	Yes	Yes	Yes	Yes	Yes
Moderate or severe renal impairment	Yes	Yes	Yes	Yes	Yes
End-stage renal disease	Yes	Yes	Yes	Yes	Yes
Seizure	Yes	Yes	Yes	Yes	Yes
Seizure disorder	Maybe	Unlikely	Unlikely	Unlikely	Unlikely
Hepatic impairment via Child-Pugh score	Maybe	--	--	--	--
Hepatic impairment via diagnosis	Yes	Yes	Yes	Yes	Yes
Central nervous system tumour	Yes	Yes	Yes	Yes	Yes
Substance use/abuse	Limited	Limited	Limited	Limited	Limited
Acute opiate withdrawal	Limited	--	--	--	--
Acute alcohol or benzodiazepine withdrawal	Limited	--	--	--	--
Suicidality	Limited	Limited	Limited	Limited	Limited
Mania	Limited	Limited	Limited	Limited	Limited
Bipolar disorder	Limited	Limited	Limited	Limited	Limited
Major depressive disorder	Yes	Yes	Yes	Yes	Yes
Hepatotoxicity	Yes	Yes	Yes	Yes	Yes
Severe hypersensitivity reaction	Limited	Limited	Limited	Limited	Limited
Cardiovascular-related death	Partial	Partial	Partial	Partial	Partial
Non-fatal myocardial infarction	Yes	Yes	Yes	Yes	Yes
Non-fatal stroke	Yes	Yes	Yes	Yes	Yes
Use of naltrexone (other than Mysimba)	Yes	Yes	Yes	Yes	Yes
Use of bupropion (other than Mysimba)	Yes	Yes	Yes	Yes	Yes
Use of CYP2B6 inhibitor	Yes	Yes	Yes	Yes	Yes
Use of CYP2B6 inducer	Yes	Yes	Yes	Yes	Yes
Use of CYP2B6 substrate	Yes	Yes	Yes	Yes	Yes
Use of CYP2Db substrate	Yes	Yes	Yes	Yes	Yes
Use of medicine that lowers seizure threshold	Yes	Yes	Yes	Yes	Yes
Opioid or opiate agonist prescription or dispensing	Yes	Yes	Yes	Yes	Yes

MAOI prescription or dispensing	Yes	Yes	Yes	Yes	Yes
Pregnancy	Yes	Limited	Limited	Limited	Limited
Breastfeeding	Limited	Limited	Limited	Limited	Limited
Death	Partial	Yes	Yes	Yes	Yes
Disenrollment	Partial	Partial	Partial	Partial	Partial
Socioeconomic data	--	Partial	Partial	Partial	Partial
Laboratory results	Limited	Limited	Limited	Yes	Limited
Surgical procedures	Yes	Yes	Yes	Yes	Yes
Diagnostic testing results	Limited	Limited	Limited	Yes	Limited
Indication (reason) for treatment with Mysimba	Partial	--	--	--	--
Discontinuation and date of discontinuation of Mysimba	Calculated	Calculated	Calculated	Calculated	Calculated
Reason(s) for treatment discontinuation	Partial–no attribution	--	--	--	--
Discontinuation due to adverse event	Partial–no attribution	--	--	--	--