Title	NB-452: A cross-sectional survey to evaluate the effectiveness of the Mysimba® Physician Prescribing Checklist (PPC) among physicians in the European Union (EU)
Protocol version identifier	1.2
Date of last version of protocol	24 December 2020
EU PAS register number	Study not yet registered
Active Substance	ATC Code: A08AA62; naltrexone hydrochloride/ bupropion hydrochloride
Medicinal product	Prolonged-release naltrexone hydrochloride/bupropion hydrochloride (Mysimba®)
Product reference	EU/1/14/988/001
Procedure number	EMEA/H/C/003687/MEA/004.6
Marketing authorisation holder(s)	Orexigen Therapeutics Ireland Limited
Joint PASS	No
Research question and objectives	The aim of this study is to evaluate the effectiveness of the Mysimba Physician Prescribing Checklist (PPC) among physicians in the EU
Country(-ies) of study	Czech Republic, Poland, Hungary, Greece and Norway
Authors	Errol Gould, PhD

Marketing authorisation holder(s)

Marketing authorisation holder(s)	Orexigen Therapeutics Ireland Limited 2nd Floor Palmerston House Fenian Street Dublin 2 Ireland
MAH contact person	Errol Gould, PhD Global Head, Medical and Scientific Affairs Currax Pharmaceuticals LLC

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1. Table of contents

2. List of abbreviations

Abbreviation	Term
AE	Adverse event
BMI	Body mass index
CFR	Code of Federal Regulations
EDC	Electronic data capture
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GVP	Good pharmacovigilance practices
IEC	Independent ethics committee
MAH	Marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
Orexigen Therapeutics Ireland Limited	OTIL
PASS	Post-authorisation safety study
PPC	Physician prescribing checklist
RMP	Risk management plan
SD	Standard deviation
SmPC	Summary of product characteristics

3. Responsible parties

Responsible party	Appointed person(s)
Principal investigator	The principal investigator will be confirmed prior to study initiation
Marketing Authorisation holder contact	Errol Gould, PhD Global Head of Medical and Scientific Affairs Currax Pharmaceuticals LLC

4. Abstract

This cross-sectional, post-authorisation safety study (PASS) aims to evaluate physician receipt, knowledge, application and effectiveness in current clinical practice, of the Mysimba Physician Prescribing Checklist (PPC) (Annex 3), which is an additional risk minimisation measure in the Mysimba European Union (EU) Risk Management Plan (RMP) developed by the marketing authorisation holder (MAH). The objectives of this study are as follows.

- Assess physician awareness of receipt of the Mysimba PPC (Question 1)
- Evaluate physician knowledge and understanding of the information within the PPC (Questions 2-10)
- Assess utilisation of the PPC in clinical practice through self-reported responses (Questions 11-12)

Study design

This PASS consists of a cross-sectional survey to be conducted amongst physicians sent the PPC to evaluate physician understanding, application, and effectiveness of the PPC in current clinical practice.

Population

The population will be comprised of physicians who have been sent the PPC in the following countries: Czech Republic, Poland, Hungary, Greece and Norway.

Variables

To address the study objectives, subject to data and variable availability from the mailing database used the following analysis will be derived from the survey data as follows:

- Physician characteristics variables for eligible responders including:
    - Country
    - Medical specialty (e.g., primary care/general practitioner, endocrinologist)
    - Years in practice
    - Practice setting (e.g., academic centre, private practice, community-based centre)
    - Number of patients prescribed Mysimba
- Variables to meet the study objectives:
    - Response to survey question regarding receipt of the PPC (Question 1)
    - Response to survey questions regarding general PPC knowledge (Questions 2-5)

- Response to survey questions about the contraindications, precautions and warnings on the use of Mysimba (Questions 6-9)
- Response to survey questions about the factors that increase risk of adverse reactions (Question 10)
- Response to survey questions regarding use of the PPC in clinical practice (Questions 11-12)

Data sources

A self-administered, web-based survey including a variety of closed-ended questions with pre-defined answers and multiple response choices will be used to collect the source data.

Study size

This study aims to collect a target total of 200 completed surveys across the participating countries with a target minimum of 20 completed surveys per country. However, reasonable efforts will be made to have a geographically representative sample.

Statistical methods

Categorical data will be summarised with frequencies, percentages, and 95% confidence intervals for percentages. Continuous data will be summarised with the following descriptive statistics unless otherwise noted: number of observations, mean, standard deviation (SD), median, minimum, and maximum.

The statistical analysis will include descriptive statistics of survey administration, invited physicians, survey respondents, and physician understanding, application, and effectiveness of the PPC in current clinical practice. Descriptive statistics will be performed on each survey question and pooled across all countries.

The physician scores (total; general PPC knowledge; factors that increase risk of adverse reactions; contraindications, precautions, and warnings) will be summarised by score, percentage, 95% confidence interval for percentage, and percentage of physicians whose total score on general PPC knowledge and risk-related questions (Questions 2-10) is at least 80% (the minimum threshold for successful survey response).

Milestones

The survey is estimated to launch in Q12021. A final report will be submitted to the European Medicines Agency (EMA) four months after the database is locked.

5. Amendments and updates

Amendments and updates will be documented using the example table provided below.

Number	Date	Section of study protocol	Amendment or update	Reason
0.1	22 October 2020		Update	EU countries to be utilized where significant use of Mysimba has occurred Use of Survey Monkey to collect data

0.2	24 December 2020		Update	Due to data availability issues the contact strategy for approaching relevant physicians as well as the planned analysis variables. Some minor typographical errors have been corrected and clarified.

6. Milestones

Milestone	Planned date(s)
Start of data collection	Q1 2021
End of data collection	Q2 2021. Each country will field the survey for up to a 60-day period.
Registration in the EU PAS register	Q1 2021
Final report of study results	Four (4) months following database lock

7. Rationale and background

Mysimba is indicated, as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients (≥18 years) with an initial Body Mass Index (BMI) of ≥30 kg/m^2 (obese), or ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of one or more weight-related co-morbidities (e.g., type 2 diabetes, dyslipidaemia, or controlled hypertension). Treatment with Mysimba should be discontinued after 16 weeks if patients have not lost at least 5% of their initial body weight.

Mysimba received Food and Drug Administration (FDA) approval in September 2014 and is available in the United States under the trade name of Contrave® extended-release tablets.

Mysimba was approved by the centralised procedure in the EU in March 2015. An RMP has been developed for Mysimba by the MAH to address the safety concerns of the product. Per the RMP, the PPC is a risk minimisation tool to help prevent the prescription of Mysimba to patients who are at an increased risk of side effects (e.g., seizures) or patients who do not meet the approved indications. This educational supplemental tool was designed to help physicians assess the suitability of patients for Mysimba prescriptions by raising awareness about patients who should be prescribed Mysimba with caution, as well as patients who should not be prescribed Mysimba. Implementation of the PPC in each EU country is dependent upon agreement between the MAH and the national authorities but must be completed prior to commercial availability of Mysimba in each country. The PPC is distributed along with the SmPC to all potential prescribing physicians of Mysimba to reinforce safe and effective use of the product. Mysimba was launched in the Czech Republic, Hungary, Poland and in Greece in January 2017 and Norway in November 2017.

Through use of the PPC, the physician is counselled to make a proper evaluation of the possible risks and benefits of Mysimba. The PPC is designed to provide important information such as the indication, contraindications, as well as a summary of important factors that may increase risk of adverse reactions. These include depression, history of mania, angina, moderate renal insufficiency, mild or moderate hepatic impairment, and concomitant use of medications that may lower seizure threshold. As mentioned, the PPC is also intended to support the proper identification of patients for whom Mysimba would be an appropriate treatment. There are also prompts embedded in the PPC to remind physicians to review the SmPC for complete prescribing details with highlighting of the relevant SmPC section (e.g. Section 4.4). Physicians are asked to review the checklist before prescribing Mysimba to make certain that they understand important criteria for patient selection to ensure safe use during the drug escalation and maintenance phases of treatment with Mysimba.

As defined in this protocol, the aim of this study is to assess the effectiveness of the PPC through evaluation of physician awareness and utilisation of the PPC, knowledge of the contraindications, warnings, precautions of Mysimba, knowledge of factors that may increase the risk of adverse reactions, and impact upon a physician's behaviour with respect to mitigating the risks in patients receiving Mysimba therapy.

This non-interventional study is designated as a Post-Authorisation Safety Study (PASS) and is a category 3 commitment to the EMA by the MAH.

8. Research question and objectives

This study aims to evaluate physician receipt, knowledge, application and effectiveness in current clinical practice, of the Mysimba PPC (Annex 3), which is an additional risk minimisation measure for Mysimba.

Specifically, this study will focus on the following research objectives:

- Assess physician awareness of receipt of the Mysimba PPC (Question 1)
- Evaluate physician knowledge and understanding of the information within the PPC (Questions 2-10)
- Assess the utilisation of the PPC in clinical practice through self-reported responses (Questions 11-12)

9. Research methods

9.1 Study design

To assess physician understanding of the Mysimba PPC, an effectiveness evaluation will be conducted using a cross-sectional design. Data collection will be conducted via a web-based survey (Annex 4) from a sample of Mysimba prescribing physicians that were sent the PPC in each of the participating study countries. A target sample size of 200 survey responses from prescribing physicians will be collected with a target minimum of 20 completed surveys per country. The survey will be conducted in the EU countries where Mysimba has launched and has sufficiently high prescription rates. The list of proposed participating countries is as follows: Czech Republic, Poland, Hungary, Greece, and Norway.

Invitations (Annex 5) will be sent out to physicians from each participating country. Due to the lack of a single database recording all patients prescribing Mysimba in the EU, it is not possible to plan for a target number of physicians to be contacted. Instead marketing partners within each of the countries considered in this study will contact physicians individually who are known to be Mysimba prescribers. Over the past more than 4 years, a significant number of physicians have gained clinical experience with the product and the contents of the PPC.

A database of all contacted physicians will be routinely updated with responders and, after each mailing, the database will be cross checked with any correspondence that had incorrect contact details such as an invalid address. To meet the target goal of completed surveys, 2 regular follow-ups will be sent to non-responders. The number of follow-ups may be increased subject to the level of the response rate at predefined recruitment milestones identified by the project team and the MAH. Each invitation sent to the random sample of physicians will include the reason for the voluntary survey, specific online access instructions, as well as a unique identification code (combination of first name, last name and postcode of the praxis/organization). Unique codes are assigned to each physician to ensure that the survey is accessed only once. All correspondence with physicians during this outreach will be conducted in the local country language to enhance comprehension of the materials. Eligible physicians who complete the survey may be reimbursed for their time spent completing the survey per each country's regulations and local laws.

Guidance provided with the PPC will encourage physicians to complete the PPC for all patients evaluated for treatment with Mysimba and to keep completed PPC forms in the patient's medical chart. The survey instrument will assess their understanding of the PPC through evaluation of responses to clinical scenarios as well as questions relating directly to PPC content knowledge.

The measure of success of the application of this risk minimisation tool will be based on a minimum acceptable threshold of understanding. This is defined as 85% of physicians whose correct response rate for the general PPC knowledge and risk-related questions (Questions 2-10) is at least 80%, or a score of 20 out of 25 possible points. Approximately 200 completed surveys are required in total, pooled across all participating EU countries, to estimate the prevalence of response to specific risk-related questions, with a precision of 5% (or 95% confidence interval ranging from 80% to 90%).

9.2 Setting

Physicians from the Czech Republic, Poland, Hungary, Greece and Norway, who were sent the PPC, will be invited to participate in the survey and constitute the study population. Other countries may be added as needed to meet enrolment requirements. In each country, only those physician specialties merited to prescribe Mysimba in each country will be invited to participate in the survey.

Table 1 below shows the proposed timeline for survey launch in each participating country.

Table 1. Survey Launch Timelines

Participating Country	**Approximate Survey Start Date**
Czech Republic	Q1 2021
Poland	Q1 2021
Hungary	Q1 2021
Greece	Q1 2021
Norway	Q1 2021

9.3 Variables

The variables for analyses will be derived from the available survey data and database variables, and will include (1) physician characteristics variables of respondents and (2) variables to address the study objectives.

- Physician characteristics variables:
    - Country
    - Medical specialty (e.g., primary care/general practitioner, endocrinologist)
    - Years in practice
    - Practice Setting (e.g., academic centre, private practice, community-based centre)
    - Number of patients prescribed Mysimba
- Variables to meet the study objectives:
    - Response to survey question regarding receipt of the PPC (Question 1)

- Response to survey questions regarding general PPC knowledge (Questions 2-5)
- Response to survey questions about the contraindications, precautions and warnings on the use of Mysimba (Questions 6-9)
- Response to survey questions about the factors that increase risk of adverse reactions (Question 10)
- Response to survey questions regarding use of the PPC in clinical practice (Questions 11-12)

The above-mentioned physician characteristic variables, if available, will also be collected for invited physicians that chose not to participate in the survey (non-respondents).

9.4 Data sources

A web-based survey will constitute the source of data collection. A sampling of physicians who were mailed the PPC will be sent a letter inviting them to participate in the survey. The survey data collection period will be open for up to 60 days in each participating country.

After the physician has logged on to the survey with the unique code found in the invitation, there will be a series of screening questions to confirm eligibility. All eligible physicians will then proceed to the survey. The survey is structured so that respondents cannot go back to a question once the question has been answered and they cannot skip ahead. The options for responses will be presented in a randomised list to minimise positional bias.

9.4.1 Eligibility criteria:

Respondents meeting these criteria will be eligible to participate:

- Respondent consents to participate
- Respondent is a physician who has prescribed Mysimba in the past 12 months

Respondents meeting these criteria will **not** be eligible to participate:

- Respondent is employed by or is a family member of someone employed by the EMA, Orexigen Therapeutics Ireland Limited, Currax Pharmaceuticals, Navamedic or Bausch Health

9.4.2 Survey Comprehension Pre-Testing

To ensure that the survey questions are clear and understood, comprehension testing will be conducted prior to launching the survey. A sample of 9-10 physicians will be asked to provide feedback on the survey. These physicians will be selected using a market research panel. One-on-one interviews will be conducted by a professional moderator specialising in qualitative research with healthcare professionals. Depending on the findings of this research, survey questions may be revised to ensure the survey content is understood.

9.5 Study size

This study aims to collect 200 completed surveys across the participating countries with a target minimum of 20 completed surveys per country. Due to the lack of a single database collecting a list of all physicians prescribing Mysimba in each country, the sponsor will collaborate with the marketing agencies Bausch Health and Navamedic to identify a sufficient number of physicians in each country so as to reach the target number of physicians required to be surveyed in this study. Table 2 below provides an estimate of the margin of error (also referred to as precision or half width of the 95% confidence interval) for varying percentages of the response (objectives) and for a target study size of 200.

If we assume that, in 85% of eligible physicians who complete the survey, knowledge with respect to important risks are in accordance with the Mysimba SmPC (a minimum score of 80% on general PPC knowledge and risk-related questions 2-10), then a study with a study size of 200 will result in a margin of error ±5% or a 95% confidence interval of 80 to 90%.

Table 2. Precision Estimates for varying percentages of the response assuming 200 completed surveys

Prevalence of response to knowledge of SmPC	Precision associated with 200 completed surveys
90%	4.2%
85%	4.9%
80%	5.5%
75%	6.0%
70%	6.4%
60%	6.8%
50%	6.9%

9.6 Data management

Physicians will enter all data into a web-based electronic database, SurveyMonkey. Prior to survey launch, user testing will be conducted consistent with quality control processes.

The SurveyMonkey system will be secured by granting access only to limited number of study staff with password-protected access based on staff roles and responsibilities. The data from the surveys collected in all countries will be aggregated for the data analysis in the final study report.

9.7 Statistical methods

9.7.1 Main summary measures

Categorical data will be summarised with frequencies and percentages. Continuous data will be summarised with the following descriptive statistics unless otherwise noted: number of observations, mean, standard deviation (SD), median, minimum, and maximum. All summary statistics carrying decimal places will be rounded to the tenth.

9.7.2 Analysis Sets

Invited Set — The Invited Set will include all physicians who were mailed the PPC and were also subsequently invited to participate in this survey.

Responder Set — The Responder Set will include all physicians who complete at least 1 Screening question.

Full Analysis Set — The Full Analysis Set will include all physicians who are eligible respondents and completed at least 1 survey question.

Completer Set — The Completer Set will include all physicians who are eligible respondents and completed all survey questions.

9.7.3 Main statistical methods

Descriptive statistics of survey administration (numbers of physicians in the Invited Set, number and percentage of physicians in the Responder Set, number and percentage of physicians in the Full Analysis Set) will be provided for the Invited Set. To the extent the

information is available, the physician characteristics of respondents (country, medical specialty, years in practice, practice setting, number of patients prescribed Mysimba) will be summarised in the Full Analysis Set. Furthermore if available, demographics of invited physicians will also be summarised for the Invited Set and Responder Set. The response to the survey questions which reflect physician understanding, application, and effectiveness of the PPC in current clinical practice will be summarised in the Full Analysis Set. Scores will be assigned to physicians who complete the survey based on the total number of correct responses to all the PPC general knowledge and risk-related survey questions (Questions 2-10) and summarised in the Completer Set.

Descriptive statistics will be performed on each survey question and pooled across all countries. The response rate for each question in the survey will be based on the total number of correct responses out of the total number of responses for that particular question. Questions 6 and 10 contain multiple sub questions; each sub question will be summarised separately. Responses to survey questions will also be summarised by demographics of respondents (country, medical specialty, years in practice, practice setting, and number of patients prescribed Mysimba).

The 12 survey questions can be further subdivided into aspects of the PPC. Specifically, survey question 1 pertains to receipt of the PPC; survey questions 2 through 5 pertain to general PPC knowledge; survey questions 6 through 9 pertain to contraindications, precautions and warnings on the use of Mysimba; question 10 pertains to factors that may increase risk of adverse reactions; and survey questions 11 and 12 pertain to self-reported utilisation of the PPC.

Physicians will also receive a percentage based on the number of correct responses achieved regarding the general PPC knowledge and risk-related survey questions 2 through 10 (defined as their score divided by 25 total points). The scores and percentages from all physicians in the Completer Set will be summarised by mean, standard deviation, median, minimum and maximum. The percentage of physicians whose score is at least 80% will also be summarised with a 95% confidence interval. The measure of success of the application of the PPC as a risk minimisation tool will be based on a minimum acceptable threshold of understanding, defined as 85% of physicians whose correct response rate for survey Questions 2 through 10 is at least 80%, i.e., a score of at least 20 out of 25 possible points.

In addition, the physician will receive a sub score pertaining to general PPC knowledge (Questions 2 through 5; 4 total points), knowledge and understanding of contraindications, precautions and warnings on the use of Mysimba (Questions 6 through 9; 13 total points), and knowledge and understanding of factors that increase risk of adverse reactions (Question 10; 8 total points). These sub-scores will be summarised as a sensitivity analysis.

Descriptive summaries of Questions 1, 11, and 12 will also be presented, even though physicians do not receive any points for answering these questions.

The software used for all summary statistics and statistical analyses will be SAS® (v9.2 or later, SAS Institute, Cary, USA).

9.7.4 Missing data

There will be no imputation for incomplete or missing data.

9.7.5 Sensitivity analyses

Sensitivity analyses will be performed as described in Section 9.7.3. Additional sensitivity analysis may be performed on the physician scores in the Full Analysis Set, if deemed significantly different from the Completer Set.

9.7.6 Interim analyses

There are no planned interim analyses.

9.7.7 Tables, Listings, and Figures

The tables, listings, and figures will reflect the planned analyses at the time of the protocol approval and may be subject to minor modifications (e.g., title and footnote changes, reordering of the output) during the actual programming without the need to amend the protocol. Variables related to physician characteristics will be summarized subject to the availability of data.

Tables

- Invited Set
    - Survey administration
    - Summary of physician characteristics

- Responder Set
    - Summary of screening question responses
    - Summary of screening question responses by country
    - Summary of physician characteristics

- Full Analysis Set and Completer Set
    - Summary of physician characteristics
    - Summary of screening question responses
    - Summary of screening question responses by country
    - Summary of survey question responses
    - Summary of survey question responses by country
    - Summary of survey question responses by medical specialty
    - Summary of survey question responses by practice setting
    - Summary of survey question responses by number of patients prescribed group

- Completer Set
    - Summary of physician score (Primary analysis)
    - Summary of physician score – Stratified by recall of receiving PPC (Question 1)
    - Summary of physician score – General PPC knowledge
    - Summary of physician score – Contraindications, precautions and warnings
    - Summary of physician score – Factors that increase risk of adverse reactions

Listings

- Responder Set
    - Screening question responses by country

- Full Analysis Set
    - Screening question responses by country
    - Survey question responses and scores

9.8 Quality control

Each respondent to the survey will enter their unique ID and then proceed to enter all data. The survey programming will not allow respondents to return to a question once the question has been answered. In addition, respondents cannot skip ahead. They are also required to complete the survey at point of initial access and are not able to stop and go back to complete the survey at a later time. Response options presented in a list will be presented in random order each time the survey is administered to minimise positional bias.

9.9 Limitations of the research methods

The following are potential limitations of the study:

- Low response due to limited market uptake of Mysimba.
- Low response due to the lack of a single database recording all physicians prescribing Mysimba. Cross-sectional study design allows for only a 'snap-shot' at a specific point in time. As prescribing physicians become more experienced with the product the responses to certain questions might change.
- Physicians from a limited number of countries will be surveyed. This may limit the generalisability of the results to other countries, particularly those outside the EU.
- Potential for bias in those eligible responders (prescribers) being more aware of the PPC and risks associated with Mysimba. The MAH is obliged to provide the PPC to all anticipated Mysimba prescribers; therefore, a control group consisting of Mysimba prescribers that did not receive the PPC cannot be included in this study design.

9.10 Other aspects

Not applicable.

10. Protection of human subjects

10.1. Physician information and consent

At the start of the survey, all voluntary respondents will be asked to provide acknowledgement of consent prior to completing the survey. The consent process will be conducted electronically. All participant identifying information will be stored separately from the actual survey data. Survey data will be anonymous to the MAH. All study team members will ensure protection of physician personal data.

10.2. Patient withdrawal

As there are no patient data being collected, this is not applicable.

10.3. Independent Ethics Committee (IEC)

The Principal Investigator will ensure that all regulatory and ethical requirements are followed in each participating country.

10.4. Ethical conduct of the study

During the conduct of this PASS study, in addition to adhering to country-specific regulatory requirements, the following will be used as sources for research practices: Guideline on Good Pharmacovigilance Practices (GVP) Module XVI- Risk Minimisation Measures: Selection of Tools and Effectiveness Indicators, European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology and Guideline on good pharmacovigilance practices Module VIII – Post-authorisation safety studies.

11. Management and reporting of adverse events/adverse reactions

Since data will be collected using a web-based survey, it is not expected that a safety event may be identified.

However, the designated study team will receive appropriate adverse event training in accordance with Orexigen Therapeutics Ireland Limited's (OTIL's) standard procedures. If a respondent reports an adverse event associated with the use of Mysimba, the study team will follow standardised adverse event (AE) training practices and inform Orexigen within 24 hours of becoming aware of the adverse event. Please see form attached as

Annex 6. The form can also be found online (http://www.cioms.ch/index.php/cioms-form-i).

12. Plans for disseminating and communicating study results

No study progress or interim progress reports will be submitted during the duration of the study. A final report will be submitted to EMA and, if necessary, to the national competent authority of countries in which the study was conducted, approximately four months following database lock.

13. References

1. Mysimba® Prolonged-Release Tablets. Summary of Product Characteristics (August 2020)
2. Guideline on Good Pharmacovigilance Practices Module XVI (Risk minimisation measures: Selection of tools and effectiveness indicators (Rev 2 Mar 2017)
3. Guide on Methodological Standard in Pharmacoepidemiology. European Medicines Agency (EMA), European Network of Centres for Pharmacoepidemiology (ENCePP); Rev 6 Jul 2017. (http://www.encepp.eu/standards_and_guidances)
4. Guideline on good pharmacovigilance practices Module VIII – Post-authorisation safety studies (Rev 3, Oct 2017)

Annexes

Annex 1. List of Stand-alone Documents

None

Annex 2. ENCePP Checklist for Study Protocols

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

Study reference number: NB-452

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 Study progress report(s)	☒	☐	☐	12
1.1.4 Interim progress report(s)	☒	☐	☐	12
1.1.5 Registration in the EU PAS register	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
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)	☒	☐	☐	9.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	9.1
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1

[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.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☐	☐	☒	
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
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)	☒	☐	☐	11

Comments:

The study does not collect and/or evaluate measures of occurrence or association of any medicinal products. Rather, the study aims to evaluate physician receipt, knowledge, application and effectiveness in current clinical practice, of the Mysimba Physician Prescribing Checklist (PPC), via an online survey.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.4
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	6
4.2.2 Age and sex?	☐	☐	☒	
4.2.3 Country of origin?	☒	☐	☐	9.2
4.2.4 Disease/indication?	☐	☐	☒	
4.2.5 Duration of follow-up?	☐	☐	☒	
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

Comments:

The study does not collect and/or evaluate data on age, sex, disease/indication, or duration of follow-up because this is not a study involving a population being treated with any medicinal products. Rather, the study aims to evaluate physician receipt, knowledge, application and effectiveness in current clinical practice, of the Mysimba Physician Prescribing Checklist (PPC), via an online survey. The age and sex of the physician (population) is not relevant to 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)	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

Study does not involve exposure to any medicinal products.

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?	☒	☐	☐	8.0
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.7.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.5
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

The study does not collect information Health Technology Assessments because the study does not include exposure to any medicinal product.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☒	☐	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.1, 9.8, 9.9
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9
7.3 Does the protocol address the validity of the study covariates?	☐	☒	☐	

Comments:

The nature of the collected data and analyses does warrant evaluation of confounding by indication. The study covariates are simple categorical descriptors of the physician's

completing the survey study. As such, the validity of these covariates are not addressed.

Section 8: Effect 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)	☒		☐	9

Comments:

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)	☐	☐	☒	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☐	☐	☒	
9.1.3 Covariates?	☒	☐	☐	9.3
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)	☐	☐	☒	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates?	☒	☐	☐	9.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.6

Comments:

No coding systems are using in this study. The study does not collect exposure or outcomes because the study does not evaluate any medicinal product. Rather, the study aims to evaluate physician receipt, knowledge, application and effectiveness in current clinical practice, of the Mysimba Physician Prescribing Checklist (PPC), via an online survey.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7.1
10.3 Are stratified analyses included?	☒	☐	☐	9.7.7
10.4 Does the plan describe methods for adjusting for confounding?	☐	☒	☐	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.4
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

The simplicity of the collected data and analysis does not warrant adjustment for confounding.

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?	☒	☐	☐	9.6
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Due to the nature of the study, there will be no independent data monitoring or safety committee established.

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?	☒	☐	☐	9.9
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)	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.1

Comments:

There is no planned analyses for residual/unmeasured confounding.

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.3

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	9.6, 10

Comments:

Due to the nature of the study design and collected data independent ethic review is not required. As a result, there are no ethical review outcomes expected.

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?	☐	☒	☐	

Comments:

No publications are planned at this time.

Name of the main author of the protocol: Errol Gould, PhD

Signature: _____ Date: 24 December 2020

Annex 3. Mysimba Physician Prescribing Checklist

Physician Prescribing Checklist Mysimba®(naltrexone/bupropion)

Mysimba is indicated, as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients (≥ 18 years) with an initial Body Mass index (BMI) ≥ 30 kg/m^2 (obese), or ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of one or more weight-related co-morbidities (e.g. type 2 diabetes, dyslipidaemia, or controlled hypertension). Treatment with Mysimba should be discontinued after 16 weeks if patients have not lost at least 5% of their initial body weight (see Section 5.1).

Patient details

If female, check whether there is any possibility of pregnancy as Mysimba must not be taken during pregnancy or when breast-feeding

Male ☐ Female ☐

Age (yrs) ☐ Weight (kg) ☐ Height (m) ☐ BMI (kg/m^2) ☐

Hypertension ☐ Hypercholesterolaemia ☐ Other CHD risk factor ☐

Smoking ☐ Low HDL cholesterol ☐

Diabetes ☐ Hypertriglyceridaemia ☐ Current BP (mm Hg) ☐/☐

Does the patient have:	**No**	**Yes**	
Uncontrolled hypertension?	☐	☐	Contraindications DO NOT PRESCRIBE Mysimba if you tick any of these boxes
Current seizure disorder, history of seizures or known CNS tumour?	☐	☐	
Current or previous diagnosis of bulimia or anorexia nervosa?	☐	☐	
Current dependence on chronic opioids or opiate agonists?	☐	☐	
Ongoing acute alcohol, benzodiazepine or opioid withdrawal treatment?	☐	☐	
Current treatment with bupropion or naltrexone?	☐	☐	
History of bipolar disorder?	☐	☐	
Treatment with a MAOI within the last 14 days?	☐	☐	
Severe hepatic impairment or end stage renal failure?	☐	☐	

Does the patient have:	**No**	**Yes**	
Moderate or severe renal insufficiency? (*If diabetic or elderly patient or at risk for renal insufficiency, assess eGFR prior to initiating Mysimba therapy)*	☐	☐	Patients with any of these factors are at an increased risk of adverse reactions. Treatment should only be initiated or maintained after full evaluation of the possible benefits and risks and review of section 4.4 of the SmPC
Moderate hepatic impairment?	☐	☐	
Controlled hypertension?	☐	☐	
Angina or recent history of myocardial infarction?	☐	☐	
History of mania?	☐	☐	
Suicidal ideation or history of attempted suicide (particularly in young people)?	☐	☐	
Depression?			
Risk factors for seizures (such as: history of head trauma, episodes of hypoglycaemia from diabetes treatment, concomitant medication that could lower the seizure threshold such as: antipsychotics, antidepressants, antimalarials, tramadol, theophylline, systemic steroids, quinolones or sedating antihistamines?)	☐	☐	

Treat with Mysimba? Yes ☐ No ☐ **Date** dd / mm / yyyy

Discontinue treatment if there are concerns with the safety or tolerability of ongoing treatment

▼ This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse events to: [insert country reporting details]

Annex 4. Mysimba Physician Prescribing Checklist Survey (English version)

Screening Questions:

1. Do you agree to take part in this voluntary survey?
   - Yes
   - No (Terminate)

2. Which best describes your primary medical specialty?
   - Primary Care/General Practitice
   - Endocrinology
   - Gastroenterology
   - Internal Medicine
   - Physician with focus in weight loss management
   - Other, please specify:_____

3. Which best describes your practice setting?
   - Academic centre
   - Community-based centre
   - Out-patient clinic
   - Private practice
   - Centre with focus in weight loss management
   - Other, please specify:_____

4. How long have you been practicing medicine?
   - ≤5 years
   - 6-15 years
   - >15 years

5. Have you ever prescribed Mysimba®?
   - Yes
   - No (Terminate)

6. How many patients have you prescribed Mysimba® for in the past 12 months?
   - None (Terminate)
   - 1-5
   - 6-10
   - 11-14
   - 15 or more

7. Do you or any of your immediate family members work for Orexigen Therapeutics Ireland Limited, Currax Pharmaceuticals, European Medicines Agency (EMA), or Bausch Health?
   - Yes (Terminate)
   - No

Survey Questions for Eligible Respondents
[Correct responses are shown in **bold** type for the convenience of regulatory reviewers]

1. Do you recall receiving the Mysimba® Physician Prescribing Checklist?
   - Yes
   - No

2. Mysimba® is the brand name for Naltrexone hydrochloride/Bupropion hydrochloride prolonged release tablets.
   - **True**
   - False
   - I do not know

3. Mysimba® is indicated for the management of weight in adults (≥18 years) with an initial BMI ≥ 30 kg/m^2 (obese), or
   - An initial BMI ≥ 25 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of one or more weight-related co-morbidities such as type 2 diabetes, dyslipidaemia, or controlled hypertension
   - **An initial BMI ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of one or more weight-related co-morbidities such as type 2 diabetes, dyslipidaemia, or controlled hypertension**
   - None of the above
   - I do not know

4. If a patient has not lost at least _____% of their initial body weight after 16 weeks, treatment with Mysimba® should be discontinued.
   - 1
   - **5**
   - 10
   - I do not know

5. Mysimba® is indicated as an adjunct therapy with increased physical activity and a reduced-calorie diet for the management of weight loss.
   - **True**
   - False
   - I do not know

6. Which of the following factor(s)/medical condition(s) are considered contraindications for prescribing Mysimba®? (For each factor/medical condition, please select one response).

Factor/Medical Condition	Yes	No	I do not know
History of bipolar disorder	**X**		
Rheumatoid arthritis		**X**	
Severe hepatic impairment	**X**		
Controlled asthma		**X**	
Ongoing acute alcohol, benzodiazepine or opioid withdrawal treatment	**X**		
Current or prior diagnosis of bulimia or anorexia nervosa	**X**		
End stage renal failure	**X**		
Chronic bronchitis		**X**	
Current dependence on chronic opioids or opiate agonists	**X**		
Current seizure disorder, history of seizures or known CNS tumour	**X**		

7. A patient is currently being treated with bupropion for something other than weight loss management. Can Mysimba® be prescribed concurrently with bupropion?
   - Yes
   - **No**
   - I do not know

8. Treatment with Mysimba® is contraindicated when a patient has received a monoamine oxidase inhibitor (MAOI) within the past _____ days.
   - **14**
   - 21
   - 30

9. A diagnosis of uncontrolled hypertension disqualifies a patient from receiving treatment with Mysimba®.
   - **True**
   - False
   - I do not know

10. Which of the following factor(s)/medical condition(s) may put patients at an increased risk of adverse reactions while taking Mysimba®? (For each factor/medical condition, please select one response).

Factor/Medical Condition	Yes	No	I do not know
Suicidal ideation or history of attempted suicide	**X**		
Controlled hypertension	**X**		
Poor circulation in feet		**X**	
Asthma		**X**	
Angina or recent myocardial infarction	**X**		
Irritable bowel syndrome		**X**	
Depression	**X**		
Mild or moderate hepatic impairment	**X**		

11. How helpful did you find the Mysimba® Physician Prescribing Checklist in identifying patients for which the use of Mysimba would be inappropriate?
   - Extremely helpful
   - Very helpful
   - Somewhat helpful
   - Slightly helpful
   - Not at all helpful

12. **In the past 12 months,** how often have you utilised the Mysimba® Physician Prescribing Checklist when prescribing Mysimba to a patient?
   - Always
   - Most of the time
   - Sometimes
   - Rarely
   - Never
   - I do not remember

<<Final Screen Language>>

This concludes the survey. Thank you very much for your participation.

***NOTE**: In countries where respondents will receive payment for their time and effort completing this survey, there may be a required form to download or a section at the end of the survey to provide details for payment*.

Annex 5. Invitation Letter to Participate in the Study

Date
Name
Address

Invitation to Participate in the Mysimba® (naltrexone/bupropion prolonged release) Physician Prescribing Checklist Survey

Dear *(insert physician's title last name)*,

As a recipient of the Mysimba Physician Prescribing Checklist, we would like to invite you to participate in a short online research survey about the checklist. You are receiving this invitation because you are listed as a Mysimba® prescribing physician in our database. The survey will be conducted by our marketing partner Orexigen Therapeutic Ireland Limited (OTIL), a wholly owned subsidiary of Currax Pharmaceuticals LLC. Bausch Health is sending this invitation on behalf of OTIL

This survey is being conducted as a post-authorisation safety study to evaluate the effectiveness of the checklist as an educational tool that supports physician knowledge and appropriate prescribing of Mysimba®. This invitation and the associated survey are approved by the European Medicines Agency (EMA) and, where required, by the local health authorities.

Your participation in the survey is voluntary. The survey will take no longer than 15 minutes to complete and can be accessed online using the link below. Your ID code will be your first name, last name and the postal code of your praxis/organisation. This information will be validated as one of the first questions in the survey.

www.xxxxxxx.com

The survey will close on <insert date>

If you qualify to take the survey, upon its completion, you may be eligible to receive compensation in the amount of **<insert FMV for approved country>** for your time.

All information collected during completion of the survey will be kept strictly confidential.

Thank you for considering completing this survey which will help us evaluate the effectiveness of the educational tool for prescribing of Mysimba®.

In case of questions or complaints, Currax Pharmaceuticals LLC can be contacted directly by eMail DPO_privacy@currax pharma.com.

Kind regards,

<marketing partner> on behalf of
Errol Gould, PhD
Global Head of Medical and Scientific Affairs
Currax Pharmaceuticals LLC

Annex 6. The Council for International Organizations of Medical Sciences (CIOMS) Form

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITALS (First, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTOIN
										☐PATIENT DIED ☐INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY ☐LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (Include generic name)		20. DID REACION ABATE AFTER STOPPING DRUG? ☐YES ☐NO ☐NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRO-DUCTION? ☐YES ☐NO ☐NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (From/to)	19. THERAPY DURATION	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (Exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergies, pregnancy with last month of period, etc)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER	
	24b. MFR CONTROL NO.
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE ☐STUDY ☐LITERATURE ☐HEALTH PROFESSIONAL
DATE OF THIS REPORT	25a. REPORT TYPE ☐INITIAL ☐FOLLOWUP