PASS information

Title	Effectiveness of the Mysimba® Physician Prescribing Checklist (PPC): Focus groups to assess understanding, attitude, and behaviour for usage of the PPC and for key safety messages (study NB-453)
Version identifier of the final study report	1.0
Date of last version of the final study report	*October 23, 2023*
EU PAS register number	EUPAS103748
Active substance	Naltrexone hydrochloride / bupropion hydrochloride ATC Code: A08AA62
Medicinal product	Prolonged-release naltrexone hydrochloride/bupropion hydrochloride (Mysimba®)
Product reference	EU/1/14/988/001
Procedure number	EMEA/H/C/003687/II/0054
Marketing authorisation holder(s)	Orexigen Therapeutics Ireland Limited
Joint PASS	No
Research question and objectives	*Research question:* What are the reasons for lack of knowledge and usage of the Mysimba® PPC among prescribers as well as for inadequate understanding of selected key safety messages? *Objectives:* 1. To identify the reasons for low awareness and usage of the PPC; 2. To assess the understanding of the cardiovascular risk factors, hepatic impairment messages, and the other less understood key safety messages, as perceived by the prescribers being interviewed; 3. To determine prescribers' attitude/agreement with the key safety messages; 4. To identify problems in the understanding of the cardiovascular risk factors, hepatic impairment messages and other less understood key safety messages; 5. To obtain insights from prescribers into the observed post-marketing reports of contraindicated concomitant opioid use; 6. Based on findings, to discuss strategies to improve awareness and understanding of key safety messages.
Country(-ies) of study	Czech Republic, Greece, Norway
Author	Yola Moride, PhD YOLARX Consultants, SAS 101 rue de Sèvres 75279 Paris CEDEX 6, France E-mail: yola.moride@yolarx.com

Marketing authorisation holder(s)

Marketing authorisation holder(s)	Orexigen Therapeutics Ireland Limited 2nd Floor, Palmerston House, Fenian Street, Dublin 2 Ireland
MAH contact person	Michael Kyle, MD Chief Medical Officer Currax Pharmaceuticals LLC e-mail: mkyle@curraxpharma.com

Table of contents

Appendices

List of tables

List of figures

1. Abstract

Title

Effectiveness of the Mysimba® Physician Prescribing Checklist (PPC): Focus groups to assess understanding, attitude, and behaviour for usage of the PPC and for key safety messages (Study NB-453)

Date: October 23, 2023
Main author: Yola Moride PhD, YOLARX Consultants

Keywords

Additional risk minimisation measures; Physician Prescribing Checklist; Focus Groups; Qualitative Research; Post-authorisation safety study

Rationale and background

Mysimba® (naltrexone/bupropion) is indicated in the EU as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adults. As per the EU RMP, the additional risk minimisation measure (aRMM) consists of a Physician Prescribing Checklist (PPC), which was distributed at product launch, following approval by each national competent authority.

A cross-sectional survey of Mysimba® prescribers was conducted in 2021 to evaluate the effectiveness of the PPC (EUPAS42491, Study NB-452) in Czech Republic, Greece, Hungary, Norway, Poland – overall, 71.3% of participants met the knowledge and understanding (KAU) criteria, which did not reach the pre-specified threshold of 85% for effectiveness and, only 58.7% remembered the PPC. A root cause analysis of low awareness of the PPC and sub-optimal KAU of selected key safety messages was deemed necessary to inform the needs and targets for improving the risk minimisation strategy. In addition, there have been observed post-marketing cases of concomitant use of Mysimba® and opioids. Although in the NB-452 survey most respondents (>94%) answered correctly the questions related to this safety concern, a root cause analysis of potential reasons for such concomitant use was also deemed necessary.

Research question and objectives

Research question: What are the reasons for lack of knowledge and usage of the Mysimba® PPC among prescribers as well as for inadequate understanding of selected key safety messages?

Primary objectives:

1. To identify the reasons for low awareness and usage of the PPC;
2. To assess the understanding of the cardiovascular risk factors, hepatic impairment messages, and the other less understood key safety messages, as perceived by the prescribers being interviewed;
3. To determine prescribers' attitude/agreement with the key safety messages;
4. To identify problems in the understanding of the cardiovascular risk factors, hepatic impairment messages and other less understood key safety messages;

5. To obtain insights from prescribers into the observed post-marketing reports of contraindicated concomitant opioid use;
6. Based on findings, to discuss strategies to improve awareness and understanding of key safety messages.

Study design

Qualitative research study through online focus groups of Mysimba® prescribers in Czech Republic, Greece, Norway.

Setting

Outpatient, all relevant specialties.

Subjects and study size, including dropouts

Maximum variation purposive sample of prescribers according to specialties and settings. It was not feasible for privacy reasons to target participants in the NB-452 survey, previously conducted in 2021. In each country there were two focus groups of 2-5 participants (total: 22 participants).

Variables and data sources

Theoretical insights (themes and domains) were generated through the analysis of verbatims and interaction reports.

Results

Most participants from Czech Rep and Greece recalled having received the PPC at the time of market launch, which was not the case in Norway because it was only accessible on the *Felleskatalogen* (Norwegian Pharmaceutical Directory) website, as requested by the Norwegian regulatory agency. Although not all focus group suggestions can or should be implemented, below are the recommendations made by the focus group participants to improve the distribution and usefulness of the PPC:

- To format the safety topics as a list of statements instead of questions in the PPC
- To improve the title to highlight the PPC objectives
- To make the PPC available in an electronic format with integration into the prescription medical records system *(to be discussed with local partners before possible implementation)*
- To improve the translation into local languages *(to be discussed)*
- In Norway, to position the PPC in a more visible location in *Felleskatalogen (to be discussed)*

Issues related to PPC awareness and/or usage were the most probable reasons for lack of knowledge and understanding of some key safety messages that was observed in the NB-452 survey, such as contraindicated concomitant use of bupropion and number of days since MAOI discontinuation. The current study also uncovered that further clarification would be required for safety messages on controlled/uncontrolled hypertension, recent myocardial infarction, and depression; participants recommended to address those by adding definitions and examples of brand name products where appropriate. On the other hand, apparent lack of knowledge of the message on hepatic impairment is likely due to the NB-452 survey question that was incorrect. All participants had a very good understanding of the contraindicated concomitant use of Mysimba® and opioids. In their opinion,

potential reasons for such concomitant use do not pertain to the PPC but rather to a lack of knowledge that a patient is using opioids.

Discussion

Based on outputs of the focus groups, the MAH plans to reformat the PPC by modifying the title with a clarification on the purpose of the PPC and phrasing safety messages as statements instead of questions, with grouping by themes. Other recommendations emerging from the focus groups, such as adding definitions and brand names, are not considered appropriate in order to maintain alignment with the SmPC. It is planned to disseminate the updated (reformatted) PPC at the next opportunity agreed with EMA, once approved by EMA and national competent authorities in each country where Mysimba® is launched. The feasibility of an electronic distribution of the PPC will need to be determined for each country where Mysimba® is launched, based on discussions with local distribution partners. These findings and resulting modifications of the aRMM will likely contribute to the appropriate use of Mysimba® and to maintaining the positive benefit-risk balance of the product.

Marketing Authorisation Holder(s)

Orexigen Therapeutics Ireland Limited

Names and affiliations of principal investigators

Not applicable.

2. List of abbreviations

aRMM	Additional risk minimisation measure
BMI	Body mass index
CIOMS	Council for International Organizations of Medical Sciences
EMA	European Medicines Agency
EU	European Union
GP	General practitioner
HCl	Hydrochloride
KAU	Knowledge and understanding
kg	Kilogram
m^2	Square meter
MAH	Marketing authorisation holder
MAOI	Monoamine oxidase inhibitor
mg	Milligram
PASS	Post-authorisation safety study
PPC	Physician Prescribing Checklist
Q&A	Questions and answers
RMP	Risk management plan
SmPC	Summary of Product Characteristics
SSRI	Selective serotonin reuptake inhibitor

3. Investigators

Not applicable.

4. Other responsible parties

Contract Research Organisations (CROs) for focus group conduct:

Brandity AS Vaskerelven 39
5014 Bergen, Norway

Pharma Easy Access
Ag. Georgiou & Irous str.
19009 Rafina, Greece

CONFESS Research
Vítkova 32/5, 186 00 Praha 8-Karlín
Czech Republic

Contract Research Organisation for qualitative analysis:

YOLARX Consultants
101 rue de Sèvres
75006 Paris, France

5. Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	*Q1 2023*	12 April 2023	
End of data collection	*Q2 2023*	24 May 2023	
Registration in the EU PAS register	*Q1 2023*	27 Feb 2023	Upon protocol finalization and prior to the start of data collection

Milestone	Planned date	Actual date	Comments
Interim report	N/A	N/A	
Final report of study results	*12 October 2023*	*23 October 2023*	*Within 6 months of start of data collection*

N/A: Not applicable

6. Rationale and background

Mysimba® was first approved in the EU on 26 March 2015 as a fixed combination medicinal product under article 10(b) of Directive 2001/83/EC as amended. Marketing authorisation renewal with unlimited validity was granted with European Commission Decision dated 16 January 2020.

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 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity (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.

Following approval by national competent authorities, the Physician Prescribing Checklist (PPC) was distributed to all potential prescribers at the time of product launch. The PPC is an additional risk minimisation measure (aRMM) to help prevent the prescription of Mysimba® to patients who are at an increased risk of adverse events (e.g., seizures) or patients who do not meet the approved indication. A cross-sectional web-based survey of Mysimba® prescribers was conducted in 2021 (PASS protocol version 1.2 approved with procedure EMEA/H/C/003687/MEA/0004.6, EU PAS Register Number 42491, Study NB-452) to determine the effectiveness of the PPC through an evaluation of physician awareness and utilisation of the PPC in clinical practice, knowledge of the contraindications, warnings and precautions of Mysimba®, knowledge of factors that may increase the risk of adverse reactions.

The NB-452 survey was conducted in the Czech Republic, Greece, Hungary, Norway, and Poland. Of the 3,971 physicians who were invited to take part in this study, 223 (5.6%) were eligible and completed all survey questions. Overall, 58.7% recalled receiving the Mysimba® PPC. Respondents in Norway were the least likely (22.6%) and respondents in Greece (82.3%) and Hungary (100%) the most likely to recall receipt. It was noted that a recent re-distribution of the PPC by e-mail or mail to physicians in all participating countries, except for Norway, may partly explain such differences in results. The reason for the re-distribution of the PPC was an update to reflect the outcome of the II/0023 variation procedure i.e., the removal of the contraindication for patients with severe renal impairment. In Norway, the new version of the PPC was uploaded to the website of the Norwegian Pharmaceutical Compendium (*Felleskatalogen*) without a repeated distribution.

In the NB-452 survey, the measure of success of the Mysimba® PPC was based on a minimum acceptable threshold of knowledge and understanding (KAU), defined as 85% of physicians whose correct response rate for the general PPC knowledge and risk-related questions was ≥80% (a score ≥20 out of 25 possible points). Overall, this threshold was not reached. In total, 71.3% (95% confidence interval: 64.9%-77.1%) of physicians from the completer set achieved this target. The questions achieving inadequate KAU most often concerned the following medical conditions, which may put patients at increased risk of adverse reactions:

- Controlled hypertension (29.1% correct)
- Mild or moderate hepatic impairment (57.0% correct)
- Angina or recent myocardial infarction (65.5% correct)
- Depression (77.6% correct)

Further questions answered correctly by less than 80% of respondents concerned the indication and

contraindicated drug interactions:

- Concomitant bupropion use (72.6% correct)
- Monoamine oxidase inhibitor (MAOI) within the past 14 days (74.4% correct)
- Approved indication for Mysimba® use (79.8% correct)

Approximately 74.8% of respondents considered the PPC either extremely (30.9%) or very helpful (43.9%). Furthermore, 29.6% of respondents indicated they either rarely (9.4%) or never (20.2%) used it. However, it is unclear how the reported level of knowledge and understanding translates into actual prescribing behaviour. Another category 3 study, namely NB-451 Drug Utilisation and Safety Study of Mysimba®, is currently underway. The final study report is expected in December 2025 (please refer to EMEA/H/C/003687/MEA/003.11 for more details). Therefore, further data on Mysimba® usage in the EU are awaited.

Since the target level of PPC effectiveness was not reached in the NB-452 survey, the MAH was requested to propose and discuss strategies for improving the awareness, usage and understanding of the Mysimba® PPC. To address this request, the MAH conducted a root cause analysis of the reasons for lack of usage of the PPC as well as for inadequate understanding of selected key safety messages, through web-based focus group discussions (qualitative research study). The findings from the study, presented in this report, will inform on the needs and targets for improving the risk minimisation strategy.

Mysimba® is contraindicated for patients receiving chronic opiate therapy. In patients requiring intermittent opiate treatment, Mysimba® should be temporarily discontinued, and opiate dose should not be increased above the standard dose. Although in the NB-452 survey most respondents (>94%) answered correctly the two survey questions related to this safety concern, there have been observed post-marketing cases of concomitant use of Mysimba® and opioids. This safety concern was therefore also addressed in the current study to obtain the prescribers' insights into potential reasons for such concomitant use.

The current study is classified as a PASS category 3 in the Mysimba® EU-RMP and has been designed to meet the requirements of the European Medicines Agency Guidelines on Good Pharmacovigilance Practices Module VIII – Post-authorisation safety studies (revision 3, 2017) [1]. The protocol was developed using the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology [2], and the 2016 CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects [3]. This study report follows the Standards for Reporting Qualitative Research [4].

This qualitative research serves as a root cause analysis of inadequate knowledge and understanding (KAU) related to selected Mysimba® key safety messages and low usage of the PPC, that have been observed in the cross-sectional study NB-452 conducted in 2021. In addition, it provides insights into the potential reasons for the concomitant use of Mysimba® and opioids, which has been observed in the real-world setting.

7. Research question and objectives

Research Question: What are the reasons for lack of knowledge and usage of the Mysimba® PPC among prescribers as well as for inadequate understanding of selected key safety messages?

Primary objectives:

1. To identify the reasons for low awareness and usage of the PPC;
2. To assess the understanding of the cardiovascular risk factors, hepatic impairment messages, and the other less understood key safety messages, as perceived by the prescribers being interviewed;
3. To determine prescribers' attitude/agreement with the key safety messages;
4. To identify problems in the understanding of the cardiovascular risk factors, hepatic impairment messages and other less understood key safety messages;
5. To obtain insights from prescribers into the observed post-marketing reports of contraindicated concomitant opioid use;
6. Based on findings, to discuss strategies to improve awareness and understanding of key safety messages.

Pre-specified hypotheses:

Hypotheses have been put forward and used as initial theory to conduct the qualitative research. Potential root causes of lack of knowledge about the existence of the PPC included the following:

1. Prescribers are aware of the checklist, but the term "PPC" is not used by clinicians in their routine clinical practice setting;
2. Clinicians remember the PPC, but dissemination occurred too long ago, and they forgot about its existence;
3. Clinicians did not see the PPC (i.e., inadequate mode of dissemination).

Potential root causes of incorrect answers to the NB-452 KAU survey regarding key safety messages included the following:

1. Lack of use of the PPC (i.e., problem of implementation of aRMM);
2. Incorrect processing of information (i.e., problem with understanding the key safety messages);
3. Conflicting sources of information (i.e., clinicians may have been exposed to sources of information other than the Summary of Product Characteristics (SmPC) or the PPC, which may not explicitly cover the key safety messages);

4. Inadequate formulation of the questions in the NB-452 survey (i.e., problem with the evaluation method).

8. Amendments and updates

None.

9. Research methods

9.1. Study design

A qualitative study, based on a grounded theory using thematic analysis, was conducted. This study was based on primary data collection using web-based (virtual) synchronous focus groups. Grounded theory is an approach by which a theory (corresponding to the hypotheses listed in section 7) is extended from the qualitative analysis conducted on the focus group data [5]. As described below, data were analysed using a thematic analysis in order to identify, organise, describe, and report repeated patterns [6]. Study design and qualitative data analysis were guided by the Consolidated criteria for reporting qualitative research (COREQ) – a checklist for interviews and focus groups [7].

Compared to quantitative research that tests hypotheses in a representative sample of patients, a qualitative research strategy is more adapted to answer the descriptive research questions, which involve an in-depth assessment of insights. The conceptual framework is that of an inductive process whereby theoretical insights (themes and domains) are generated. Data were collected through online focus groups of Mysimba® prescribers in order to identify and explore reasons for sub-optimal usage of the PPC, inadequate KAU of selected key safety messages, and potential reasons for the concomitant use of Mysimba® and opioids. There were two focus groups in each study country (Czech Republic, Greece, and Norway) for a total of six focus groups. Maximum variation purposive sampling was attempted to ensure a representation of specialties, practice setting, and awareness/use of the PPC. For privacy reasons, it was not possible to target participants in the original NB-452 survey.

9.2. Setting

The study targeted physicians who had prescribed Mysimba® at least once in the 12 months prior to invitation, in Czech Republic, Greece, and Norway. Czech Republic was selected as it offered the largest number of NB-452 survey participants from Eastern Europe (there were three Eastern European countries included in the survey: Czech Republic, Poland, and Hungary, contributing respectively, 53, 41 and 2 physicians in the completer set). Greece was selected because it accounted for almost half of the participants in the NB-452 survey, and it represents the south of the EU. Finally, Norway was selected because, in the original NB-452 survey, respondents were the least likely to recall receipt of the PPC (22.6%), since the PPC is only available on a website in this country.

9.3. Subjects

In contrast to quantitative research that uses random sampling to ensure adequate generalisability of findings, qualitative research aims at identifying and selecting information-rich participants in order to achieve depth of understanding [8]. Because there was no trend observed in the NB-452 survey regarding awareness, knowledge and understanding by specialty or practice setting, no specific subgroup of prescribers was targeted for the focus groups. A maximum variation purposive sample was therefore attempted since the purpose was to document unique or diverse variations that have emerged in the factors influencing the understanding of the Mysimba® key safety messages, and to identify important common patterns that cut across variations [9]. Because of data privacy consideration, it was not possible to select participants on the basis of their participation or scores in the initial NB-452 KAU survey (as this information was confidential); however, previous participation in the survey was assessed and NB-452 survey questions that did not meet the set threshold of adequate KAU were administered to participants during focus group sessions.

Marketing partners in Czech Republic (Bausch Health), Greece (WinMedica), and Norway (Navamedic) were contacted to assist in the identification of potential participants. Czech Republic was the only country to use advertising to recruit focus group participants. No unblinding was necessary for the MAH.

For those who met the eligibility criteria listed below, informed consent was explained over the phone and a study information sheet, including Zoom etiquette training material, was sent by e-mail. Follow-up calls were made to review the consent form and to provide additional information regarding the use of Zoom and the date of the meeting. Study flow is summarised in Figure 1 below.

Figure 1. Study flow for virtual focus groups

Prescribers were eligible to participate in the focus groups if they met the following inclusion and exclusion criteria:

Inclusion criteria:

- Respondent consented to participate in a virtual focus group with an audio recording of the session;
- Respondent was a physician who had prescribed Mysimba® in the past 12 months;
- Respondent had access to technology (internet and e-mail).

Exclusion criterion:

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

9.4. Variables

Not applicable as this was a qualitative research study.

9.5. Data sources and measurement

Synchronous virtual focus groups were conducted through Zoom videoconferencing technology (Zoom Video Communications, Inc. San Jose, CA). The key aspect of focus groups is the interactions between participants as a way of collecting qualitative data that would not emerge using individual interviews [10]. Virtual focus groups ensure the reach of a wide geographical distribution of participants across the three countries. As described by Dos Santos Marques (2021) [11], it also allows for the collection of data in real time, as well as enable interaction between and among the participants and the moderators.

At the time of enrolment, a training on Zoom etiquette was provided to participants consisting of reminding participants to be alone in a room during the meeting, to turn their camera on, and to avoid outside distractions (e.g., mobile phones).

For security reasons, all meetings were password protected and a unique invitation was sent to participants individually. At the time of the meeting, all attendees first joined a waiting room with a co-host. In the waiting room, the participants' identity was confirmed, and their screen name was changed, allowing for confidentiality between participants. Once all the attendees joined, the meeting was locked. Sessions were audio recorded only, which preserved the identity of the participants while still allowing for data collection for qualitative analyses.

The research team included a moderator and an assistant moderator from external vendors (listed in Responsible Parties section above) who specialise in the conduct of focus groups. The moderator was responsible for facilitating the discussion, prompting members to speak, requesting overly talkative members to let others talk, and encouraging all the members to participate. Furthermore, the moderator took notes that informed potential emergent questions to ask. The moderator presented the focus group participants with a series of questions corresponding to the less well understood safety messages in the initial NB-452 KAU survey (see Document 1 of Annex 1 for focus group interview guide), and also showed participants a physical copy of the PPC as stimulus material and asked them to respond to it. The

assistant moderator recorded the session, took notes, greeted latecomers, conducted any troubleshooting, and provided verification of data, when necessary. The assistant moderator also took notes on non-verbal communication such as face expressions and reactions to other participants' comments, which were documented in an interaction report. Due to the web-based nature of the data collection, only face expressions and reactions were examined as non-verbal communication. Transcripts (verbatims) and meeting notes were then translated in English using automated procedures, followed by a manual verification of the translation.

9.6. Bias

Participant bias: Participants may have responded to the questions based on what he/she thought was the right answer or according to social acceptability or to agree with the moderator. Questions in the focus groups were open-ended in order to avoid participant from simply agreeing or disagreeing with the moderator and were not able to use a simple "yes" or "no" answer. In order to minimize social desirability or observer bias, questions were phrased in a manner to allow the participant to feel accepted, regardless of his/her answer or KAU.

Selection bias: Owing to data privacy regulations, it was not possible to target participants in the initial NB-452 KAU survey. A purposeful sample of prescribers was used for this qualitative study and none of the focus groups respondents had participated in the KAU survey - however, all were presented with the NB-452 survey questions that were less understood and were not shown the answers right away.

Researcher bias: May occur if a researcher interprets the data to support his/her hypothesis. There was no *a priori* hypothesis communicated to the moderators, and data were analysed independently by someone not involved in the interviews. Questions were kept simple, and no leading questions were used that could prompt participants to respond in favour of a particular assumption.

9.7. Study size

The aim was to include three or four participants in each focus group, which is the recommended size for a virtual focus group. Previous research has shown that virtual focus groups using web-based video conferencing platform is considered as a valid and feasible tool to collect qualitative data [12, 13]. Through additional research conducted during the COVID-19 pandemic, virtual focus groups were shown to offer the possibility to cover a wider geographical range, and feasibility is highest with three to four participants, as opposed to the minimum of six recommended for in-person focus groups [11]. A higher number of participants may result in technological difficulties (more troubleshooting during the sessions) and hamper online interactions between participants to share their thoughts, opinions, beliefs, and experiences.

There were two focus groups per study country, which is consistent with recommendations that three to six different focus groups are adequate to reach data saturation and/or theoretical saturation (i.e., when no more themes or theories emerge from the discussions) [14, 15].

9.8. Data transformation

The data analysed consisted of the translated versions (in English) of verbatims of the focus group discussions, along with field notes constructed by the moderator and assistant moderator, and any notes extracted from the debriefing meeting. Dissents and argumentative interactions between focus group participants were also documented in an interaction report to increase the richness of the data.

Because in a focus group the unit of analysis is the group and not the individual, focus group members who did not contribute to a discussion were not acknowledged, such as those who are silent (e.g., do not want to reveal that they have a different opinion, attitude or beliefs, level of knowledge, or who are uninterested to the issue being discussed, or those who agree with the majority of participants and simply nod). Consensus in the themes may be due to the group context as it does not reflect the views of the individual group members. Information on participants who did not express any views at all were therefore also analysed. Non-verbal communication, through facial expressions, was also analysed to identify acquiescence, dissent, or absence of views.

9.9. Statistical methods

9.9.1. *Main summary measures*

Not applicable.

9.9.2. *Main statistical methods*

There were no statistical analyses conducted as this was a qualitative research study. The transcripts were analysed by theme, as follows:

- Physician Prescribing Checklist: Awareness of its existence, preferred way of receiving it, usage, usefulness, suggestions for improvement
- Knowledge and understanding:
    - Mysimba® indication
    - Concomitant use of bupropion
    - Increased risk of adverse reactions for the following medical conditions:
        - Controlled hypertension
        - Angina or recent myocardial infarction
        - Depression
        - Mild or moderate hepatic impairment
    - Concomitant use of MAOI
- Concomitant opioid use: Potential reasons why this may happen

For each survey question, the following items were to be discussed (not all items were discussed within a focus group, depending on the direction taken by the discussions): Clarity of the survey question and of the PPC, agreement with the survey response, feasibility to proceed as stated in the correct answer, source of information to answer the question, communication provided by the drug manufacturer on this issue, suggestions for improvement of the PPC.

For each country, the data were analysed one focus group at a time. It was therefore possible to determine whether the themes that emerged from one group also emerged in the other group.

In addition to the above-mentioned analyses, coding of verbatims was conducted using QSR NVivo, version 14, a qualitative data analysis software that facilitates the organisation and analysis of unstructured data. However, as the autocoding provided with the software failed to generate themes, a coding structure based on themes discussed during focus group meetings was defined.

A proportion was calculated for each theme discussed, where the number of coded words for a theme was divided by the total number of coded words across all themes. This provided an estimate of the proportion of time spent discussing each theme. Similarly, a proportion was calculated for each theme category, where the number of coded words in a category was divided by the total number of coded words in the theme. Graphs were generated from the calculated proportions to visualise the most discussed themes or categories.

9.9.3. *Missing values*

Not applicable.

9.9.4. *Sensitivity analyses*

Not applicable.

9.9.5. *Amendments to the statistical analysis plan*

Not applicable.

9.10. Quality control

Verbatims were translated in English using automated procedures followed by a manual review.

To enhance the reliability of analyses, coding was performed independently by two researchers and conflicts were resolved by consensus.

9.11. Protection of human subjects

Owing to the nature of the study, ethics approval to local or national institutional review boards was not required in the study countries. All focus group participants provided written informed consent and their name or contact did not appear in any of the study materials. Participants received a compensation for their participation and payment was processed by the focus groups vendors.

10. Results

10.1. Participants

Overall, six focus groups took place between 12 April and 24 May 2023, two in each country selected, for a total of 22 participants (between two and five participants per focus group).

10.2. Descriptive data

Norway: Three physicians participated in focus group 1 (two of whom shared the same office), and two in group 2 (also sharing the same office). All were general practitioners (GPs) from primary healthcare clinics (public sector), and none had participated in the initial NB-452 survey.

Czech Republic: Four physicians participated in each focus group. In the first focus group, there were two diabetologists (one was also an endocrinologist), one obesitologist who was also a paediatrician, and one GP. All worked in the private sector, and the obesitologist/paediatrician also worked in a state facility. In the second focus group, there were two diabetologists (one was also an endocrinologist), one GP, and one had three specialties (diabetologist, endocrinologist, and internist). The diabetologist worked in a state hospital, all the others worked in the private sector. None had participated in the previous NB-452 survey.

Greece: Five physicians participated in the first focus group, and four in the second. In the first focus group, there were two internists/diabetologists, one internist who was also an obesity specialist, one endocrinologist, and one surgeon. In the second focus group, there were three internists and one GP. Across the two groups, all, except one, worked in the private sector, and none participated in the previous NB-452 study.

10.3. Outcome data

Not applicable.

10.4. Main results

10.4.1. *Themes and Coding*

In order to code verbatims using QSR NVivo, a coding structure was defined based on themes discussed during focus groups, as summarized in Table 1. The moderators' and participants' words other than those related to the themes were not considered during coding, as they had no added value for the analysis.

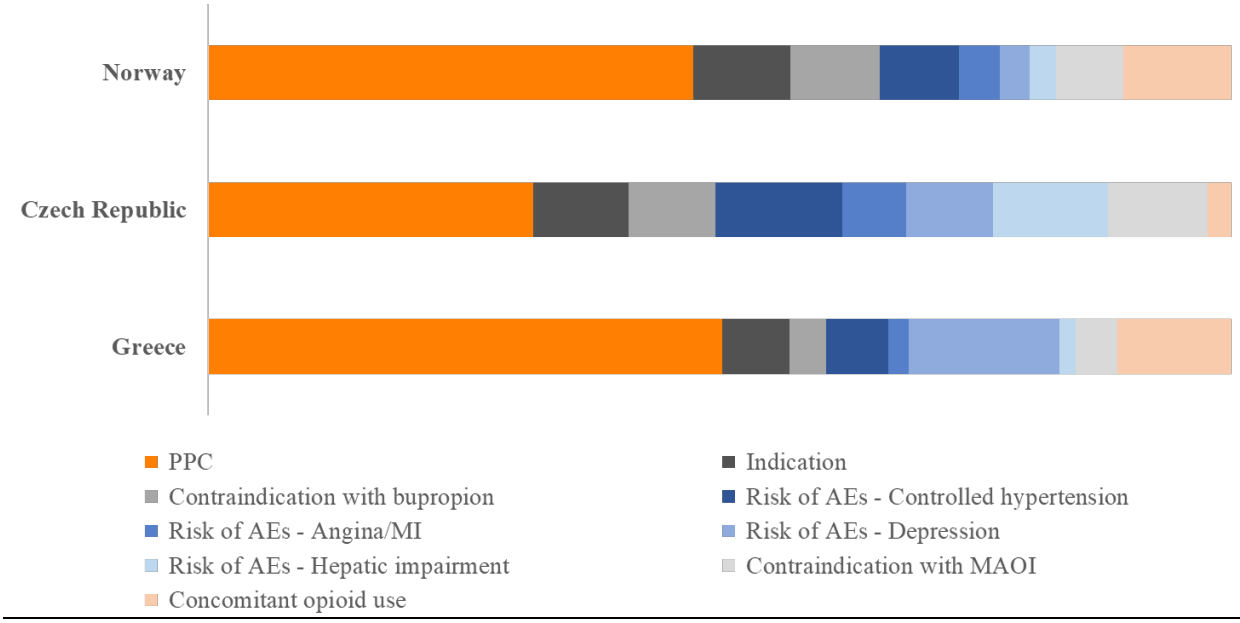
Table 1. Themes and categories defined for the coding of verbatims

Theme		Theme Categories
PPC		• Awareness: yes, no • PPC use: past or present use, never used or no current use • Relevance/usefulness: yes, no • Practical challenges: PPC format, interpretation, lack of PPC dissemination, lack of time, redundancy with other sources • Recommendations: format, dissemination
Key safety message	Mysimba® indication	• Knowledge/understanding • Misunderstanding • Existing safeguards • Practical challenges • Recommended clarifications
	Contraindication with bupropion	
	Risk of AEs with controlled hypertension	
	Risk of AEs with angina or recent MI	
	Risk of AEs with depression	
	Risk of AEs with hepatic impairment	
	Contraindication with MAOI	
Concomitant opioid use		• Knowledge of cases of concomitant use • Existing safeguards • Potential situations at risk

AEs: adverse events, **MAOI**: monoamine oxidase inhibitors, **MI**: myocardial infarction, **PPC**: Physician Prescribing Checklist

Based on the coding, the PPC was the most discussed theme across all countries (Figure 2).

Figure 2. Estimated proportion of time spent discussing themes by country



AEs: adverse events, **MAOI**: monoamine oxidase inhibitors, **MI**: myocardial infarction, **PPC**: Physician Prescribing Checklist

The next sections present, by country, the participants' characteristics and a summary of their discussion on the PPC (dissemination, usefulness, general content, and format) and on each initial NB-452 KAU

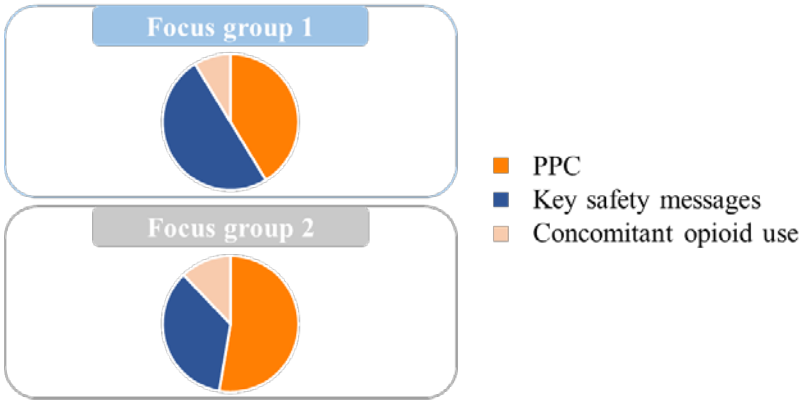
survey question, as well as their opinion on potential reasons for concomitant use of Mysimba® and opioid (interview guide available in Document 1 of Annex 1).
Then, recommendations on PPC dissemination, format, and content are made based on the participants' comments.

10.4.2. *Norway focus groups*

Themes discussed

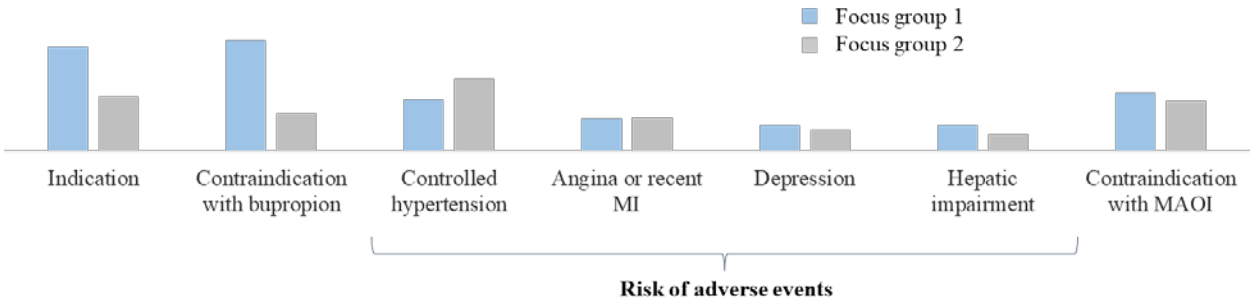
Based on the coding of verbatims with QSR NVivo, the most discussed themes in focus group 1 were Mysimba® indication and contraindicated concomitant use with bupropion, while the PPC was the most discussed theme in focus group 2 (Figure 3 and Figure 4). The estimated proportion of time spent on different topics for each key safety message is illustrated in Figure 9 in Document 2 of Annex 1.

Figure 3. Estimated proportion of time spent on themes for each focus group – Norway



PPC: Physician Prescribing Checklist

Figure 4. Estimated proportion of time spent on key safety messages for each focus group – Norway



MAOI: monoamine oxidase inhibitors, **MI**: myocardial infarction

Physician Prescribing Checklist

When asked if they had received or seen the PPC, one participant in group 1 recalled having seen it through a medical sales representative, and his/her colleague, also in group 1, was made aware of it by the other participant. The third participant had never seen the PPC. In group 2, both participants had been presented the PPC by a medical sales representative shortly before the focus group took place.
In group 1, none of the participants used the PPC, and in group 2, one participant had been using it

(through internet) since he/she recently discovered it, and the other participant was considering using it. All five participants consult *Felleskatalogen* (the Norwegian Pharmaceutical Directory) when checking for indications. However, none of them was aware that the checklist was included in *Felleskatalogen*.

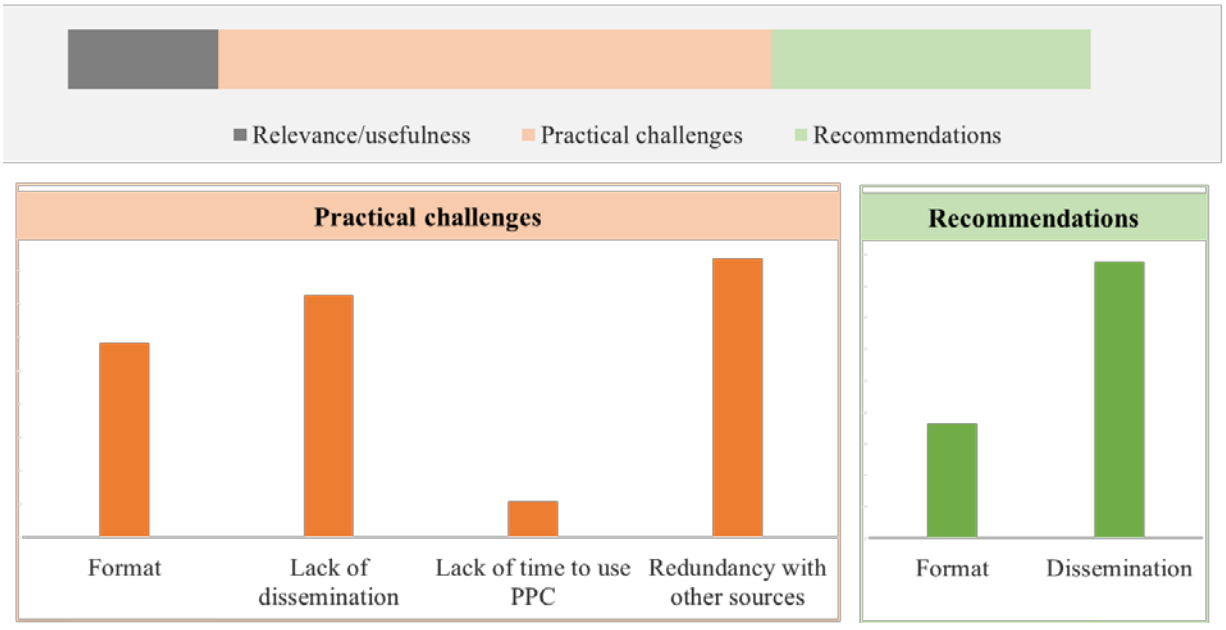
The listed reasons why physicians would not use the PPC were unawareness of its existence, lack of time, redundancy with other sources of information (*Felleskatalogen*, *Helfo* blue prescription portal – a portal for medicine fully or partially funded by the State), and its unpractical paper format. One participant mentioned that physicians sometimes get paid to fill out some prescription forms, and this could be an incentive to use the PPC.

All participants suggested that the PPC be available online, either in the *Helfo* blue prescription portal, as a pop-up window when writing a prescription, in *Felleskatalogen* (not knowing it was already available), either as a link under the contraindication section or between the indication and dosage sections, or in their journalling system.

When asked about PPC usefulness, one participant thought it was more efficient to consult the PPC than the *Felleskatalogen.* In general, participants thought that there was no need to fill out the checklist for each patient, especially if it could not be added to the patient's electronic medical records. All but one participant thought the paper format was not useful.

The estimated proportion of time spent discussing PPC relevance/usefulness, practical challenges, and recommendations is presented in Figure 5.

Figure 5. Estimated proportion of time spent on PPC topics - Norway



Mysimba® Indication

The first survey question was on Mysimba® indication. Only one of the three participants in group 1, and both participants in group 2 knew the correct answer. One participant from group 1 asked, before giving his/her answer, whether the question related to the criteria for a blue prescription (i.e., prescription for a medicine fully or partly funded by the State), which may indicate an ambiguity in Norway regarding the approved indication. Otherwise, participants did not think that the survey question was confusing

(one participant thought it was clear, the others did not comment). Participants also thought the PPC provided clear information on indication.

Participants pointed out that in order to get a blue prescription for Mysimba® in Norway, the criteria are much more restrictive than those of the approved indication. Patients need to have a BMI over 40, or over 35 with comorbidities including controlled hypertension, dyslipidaemia, or diabetes. Therefore, Mysimba® is rarely prescribed to patients with a BMI between 27 and 30, due to financial burden. According to all participants, Mysimba® could be beneficial for patients with a BMI between 27 and 30 and a comorbidity other than those mentioned above.

Concomitant Use of Bupropion

Regarding the concomitant use of Mysimba® and bupropion, participants from group 1 thought they could not, but were all hesitant, as well as one participant from group 2 (the other participant did not answer). Participants would check for interaction or maximum dose for bupropion, either in the *Interaksjoner.no* website (database of drug interactions), *Felleskatalogen*, or *Reliskatalogen.no* website (which contains a Q&A section) or would check with a colleague.

A participant suggested to include a pop-up window when writing a prescription, and another participant mentioned that for a double prescription of the same active ingredient, a notification already existed in their system, but not necessarily in all systems. Most participants thought that the concomitant use of these two drugs was unlikely to occur (they would get a pop-up message, and bupropion was not much prescribed in Norway).

All but one participant did not provide comments on the clarity of the survey question on concomitant use with bupropion; one participant thought the PPC was clear on that topic.

Medical Conditions with Increased Risk of Adverse Reactions

The four medical conditions less well understood in the initial NB-452 KAU survey (controlled hypertension, angina or recent myocardial infarction, depression, and mild or moderate hepatic impairment) that could put patients at an increased risk of adverse reactions while taking Mysimba® were discussed. One participant thought the information was clear in the PPC, others did not comment. Below is a summary of participants' responses and comments for each medical condition.

Controlled hypertension

Hypertension (controlled and uncontrolled) was the most discussed topic related to increased risks. All participants in group 1 thought that Mysimba® could not increase the risk of adverse reactions when hypertension was controlled, since the latter was part of the approved indications for Mysimba®, but that their hypertension needed to be checked regularly. They all mentioned that Mysimba® was contraindicated for uncontrolled hypertension. Both participants in group 2 thought that Mysimba® could increase the risk of adverse reactions in controlled patients. They also mentioned that, for uncontrolled patients, their blood pressure needed to be controlled before considering prescribing Mysimba®.

Angina or recent myocardial infarction

Both focus groups spent very little time on the topic of angina/recent myocardial infarction. Only one participant from group 2 was not sure whether Mysimba® could increase the risk of adverse reactions for these two conditions and mentioned that he/she would have checked before prescribing Mysimba®.

Others had already seen the PPC on that topic when the moderator asked the question, and all responded that Mysimba® was contraindicated for these two conditions.

Depression

Very little time was spent on depression as well, for both focus groups. One participant from group 1 did not comment on that question, and the other four participants provided the correct answer. Both participants from group 2 mentioned that Mysimba® could also have a positive effect on depression, since it contained an ingredient that has an antidepressant effect.

Mild or moderate hepatic impairment

In group 1, mild/moderate hepatic impairment had only been touched upon, and one participant mentioned having just seen the information on the PPC. One participant in group 2 mentioned that, for patients moderately impaired, he/she always checks if a drug new to the patient could have adverse effects. The other participant would first check for contraindications, and depending on the comorbidity, would also check for side effects.

One participant in group 2 noted that only "moderate" was listed in the current version of the PPC (i.e., "mild" was not listed). However, the NB-452 KAU survey question stated mild and moderate hepatic impairment, which suggests an incoherence between the PPC and the initial survey question.

Use of Monoamine Oxidase Inhibitor

Two participants in group 1 were aware that Mysimba® was contraindicated when a patient had used an MAOI, but only one knew the wash-out period of 14 days. They mentioned that a pop-up window would appear in their prescribing software to alert about the contraindication. One participant in group 2 thought the wash-out period was one year and mentioned that MAOIs were not often used in Norway. The other participant did not know the answer and mentioned that he/she does not prescribe MAOIs. Both participants thought the original survey question was clear, as well as the PPC on this issue.

Concomitant Use of Mysimba® and Opioids

Participants from both focus groups thought that concomitant use of Mysimba® and opioids was unlikely. In their prescribing system, a pop-up window would appear to alert them of the interaction between these two drugs. Moreover, one participant mentioned that opioids have to be prescribed (i.e., not available over the counter), and that, for opiate addicts or heavy users, losing weight was not a priority. Another participant mentioned that pharmacists normally look at the patient's medication list, and check for cautions and contraindications. According to participants, reasons for concomitant use could be that the physician has not checked or has overridden safety warnings, is unaware that the patient is taking opioids, does not know Mysimba®'s ingredients, is unaware of the contraindication, or their prescribing system does not show contraindications.

Recommendations from Norway

Below are the recommendations for the PPC dissemination based on Norway participants' comments.

1. To include the PPC as a hyperlink titled: "Checklist prior to treatment" ("sjekkliste før oppstart") in *Felleskatalogen*, in the section on contraindications, indication or dosage.

2. To integrate the PPC in the medical records system (pop-up window) to avoid redundancy and reduce the administrative burden of filling out the form.

There were no recommendations on the PPC format and content.

Summary of focus groups from Norway

The PPC appears to be a useful tool for prescribers to know the criteria that would allow them to initiate Mysimba®. The format and content are relevant to prescribers. The main issue in this country relates to the accessibility of the PPC. Awareness of the PPC should be increased by using alternative means of dissemination, such as a pop-up window in the prescribing software, in a more visible location in *Felleskatalogen*, or integrated in the medical record system of prescribers.

In the NB-452 survey question related to conditions that could increase the risk of adverse reactions, hepatic impairment included both the mild and moderate severities. However, a participant noted that the current version of the PPC refers to moderate impairment only, which revealed an issue with the initial NB-452 survey question.

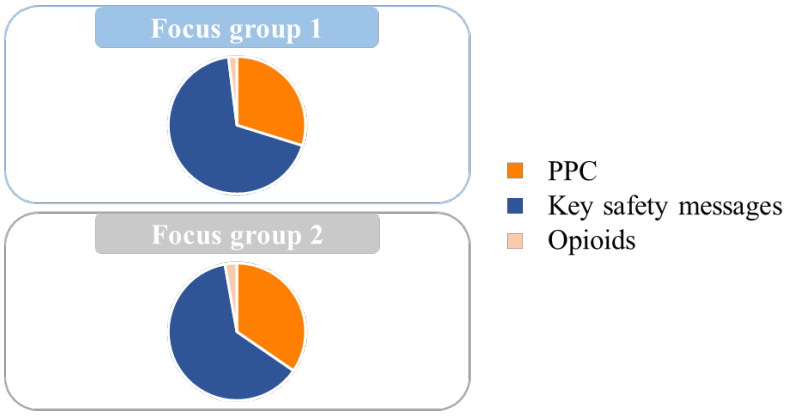
In clinical practice, in Norway, the blue prescription form is a safeguard for ensuring the appropriate use of Mysimba® as the criteria for reimbursement are stricter than those of the approved indication.

10.4.3. *Czech Republic focus groups*

Themes discussed

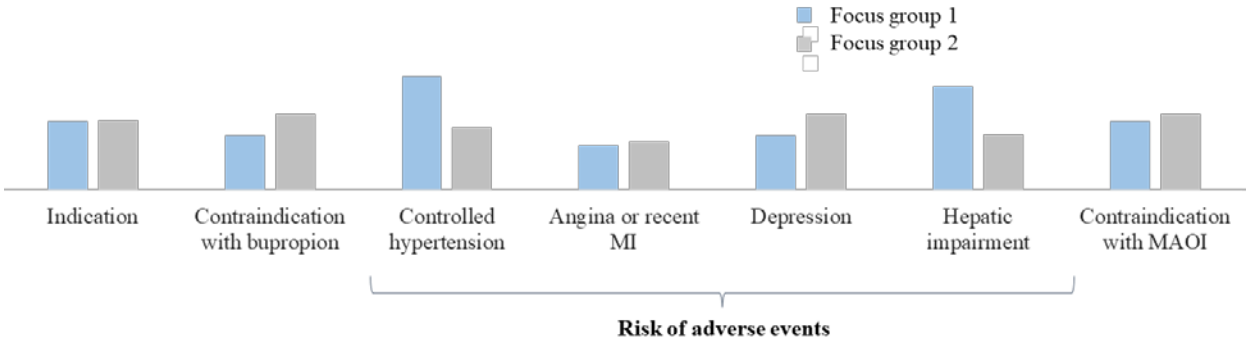
Based on the coding of verbatims with QSR NVivo, the most discussed theme in both focus groups was that of key safety messages (when grouped under one theme) (Figure 6), with all key safety messages relatively equally discussed (Figure 7). The estimated proportion of time spent on different topics for each key safety messages is illustrated in Figure 13 in Document 2 in Annex 1.

Figure 6. Estimated proportion of time spent on themes for each focus group - Czech Republic



PPC: Physician Prescribing Checklist

Figure 7. Estimated proportion of time spent on key safety messages for each focus group - Czech Republic



MAOI: monoamine oxidase inhibitors, **MI**: myocardial infarction

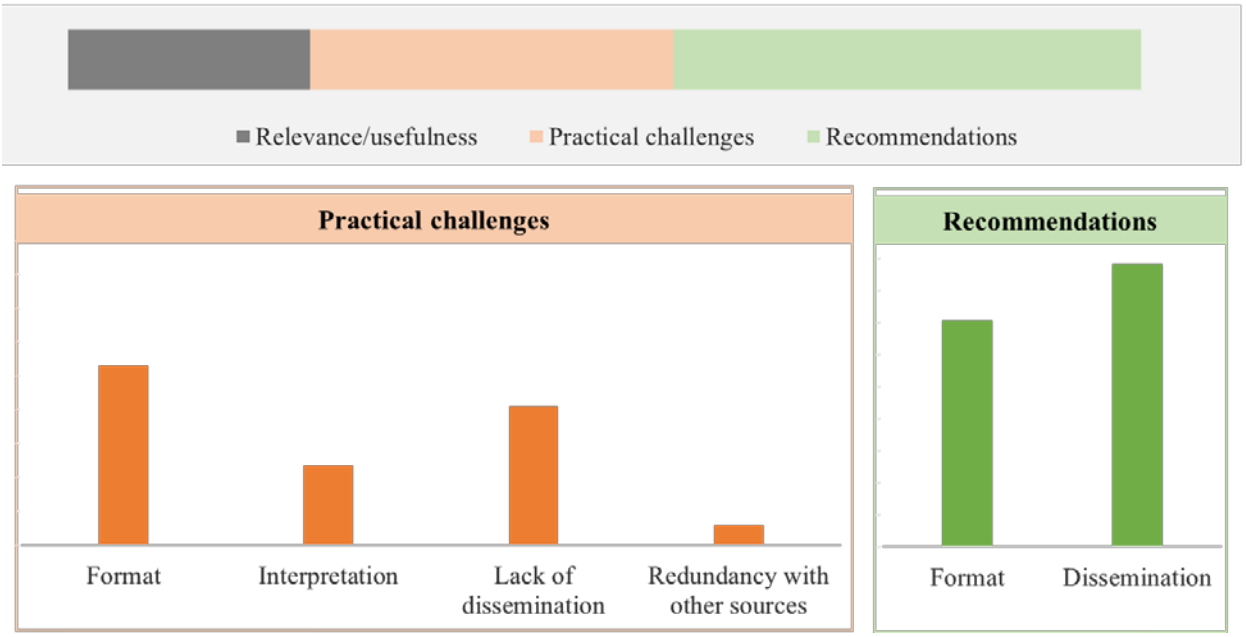
Physician Prescribing Checklist

Except for one participant in group 2 who had never seen the PPC, all participants claimed to have received it. In group 1, two received it from a medical representative, one by mail, and one at a conference, while in group 2, three participants received it from a medical representative. All participants agreed that the ideal way of obtaining the PPC would be through a medical representative. Two participants from group 1 also mentioned that an online version of the PPC would be useful. All participants who had received the PPC had used it when Mysimba® was new on the market, but no longer use it.

In general, participants from both groups found the PPC useful, well structured, and practical as important information on conditions for use of Mysimba® was well summarized. One participant from group 1 mentioned that it was quicker to refer to the PPC than the SmPC, since it is concise and clear. However, one participant from group 2 thought that the PPC should be a little more concise. This participant also suggested to write the contraindications and factors at increased risk of adverse reactions in the form of statements, rather than questions. Two participants from group 1 said the document title (i.e., Physician Prescribing Checklist) did not mean anything to them and was misleading. Another participant proposed that issues be grouped by system organ class (e.g., neurological, psychiatric).

The estimated proportion of time spent discussing PPC relevance/usefulness, practical challenges, and recommendations is presented in Figure 8 below.

Figure 8. Estimated proportion of time spent on PPC topics - Czech Republic



Mysimba® Indication

All participants from both groups knew the correct answer to the question on Mysimba® indication, and agreed with the indication, which according to them, is not restrictive. However, in group 2, two participants thought that patients with a BMI between 27 and 30 without comorbidities could also benefit from the drug. On the other hand, two participants from group 1 mentioned that they prescribe the drug to patients with a BMI higher than 29 or 30, and not to patients who are only overweight, since these patients would not pay for weight loss medication.

Participants thought the information on indication provided in the PPC was clear, as well as the NB-452 survey question.

Concomitant Use of Bupropion

On the question of concomitant use of Mysimba® and bupropion, all but one participant provided the correct answer. All participants said that they would not prescribe Mysimba® to a patient taking bupropion; and some from both groups mentioned their concern of an increased dose. However, two participants (one in each group) later said they would consult the patient's psychiatrist to obtain their approval for Mysimba® prescription. Two participants from group 1 mentioned that they utilise a system where they can verify the patient's medication records so they can see what the patient has been prescribed in the last few months.

One participant thought the original NB-452 survey question was "oddly put" and suggested that, instead of making a statement ("A patient is currently being treated with bupropion for something other than weight loss management"), and then asking the question ("Can Mysimba® be prescribed concurrently with bupropion?"), to directly ask the question, which would then be "Can Mysimba® be prescribed with bupropion, if bupropion is already being taken for a reason other than weight reduction?".

Three of the four participants from group 2 thought the question related to bupropion in the PPC ("Does

the patient have current treatment with bupropion or naltrexone?") was unclear in Czech, and that a translation should be improved.

Medical Conditions with Increased Risk of Adverse Reactions

Below is a summary of participants' responses and comments for medical conditions that could put patients at an increased risk of adverse reactions while taking Mysimba®.

Controlled hypertension

Only one participant, from group 1, knew that patients with controlled hypertension were at an increased risk of adverse reactions. All participants in group 2 and some in group 1 confused contraindication and adverse reaction, and since controlled hypertension is part of Mysimba® indication, they answered "no" to the question. For example, one participant mentioned that he/she tends to look at the question in terms of indication and contraindication, even though he/she understands how the question is worded. Another participant initially thought that the question contained an error, and that it rather referred to uncontrolled hypertension. It emerged from the discussions that the participants would have prescribed Mysimba® without acknowledging the risk because controlled hypertension was one of the comorbidities for which Mysimba® was indicated.

Some participants thought that "controlled" was not well defined in the PPC, and that treatments which could put a patient at risk should be listed. For example, one participant said he/she would only be very careful if the patient was taking betablockers. One participant pointed out that the NB-452 question was badly translated to Czech (it reads "satisfactorily controlled hypertension").

Angina or recent myocardial infarction

Only one participant from group 2 was not sure about the answer, all other participants from either group thought that angina or recent myocardial infarction would increase the risk of adverse reactions. Three participants from group 2 said they would not prescribe Mysimba® to a patient with a recent heart attack because the patient was unstable. Three participants from group 1 also commented that the cardiovascular disease had to be controlled first, and then to think about treating obesity.

In both groups, participants thought that the word "recent" was too vague, and that a period of time (e.g., within the last six months) since myocardial infarction occurred should be defined. One participant thought that the Czech translation of the survey question could be improved (it reads "suffered a myocardial infarction").

Depression

All participants from group 1 rapidly answered "yes" to the question (i.e., Mysimba® does increase the risk of adverse reactions for patients with depression). However, during their discussion, one mentioned that his/her answer would be different depending on whether the depression was treated or not, and if untreated, Mysimba® could help. Other participants also had a different opinion whether the depression was treated or not. In group 2, all participants answered "no" to the question; two of them mentioned that Mysimba® would be more likely to help. In that group too, participants had a different opinion for treated and untreated depression.

One participant from group 2 suggested to list in the PPC antidepressants that can and cannot be combined with Mysimba®.

Mild or moderate hepatic impairment

All participants from both groups agreed that patients would have a higher risk of adverse reactions on Mysimba® if their hepatic impairment was moderate, but not mild. One participant from each group said they would not prescribe Mysimba® to patients with moderate hepatic impairment. One participant from each group mentioned that having both mild and moderate in the same survey question was confusing, and that the answer would be different for mild and moderate impairment.

Use of Monoamine Oxidase Inhibitor

All participants from group 1 were unsure of the number of days that Mysimba® was contraindicated after the end of MAOI treatment, and all agreed with the survey answer. When asked if it was feasible in practice to proceed as stated in the PPC, participants responded that they would either have to check in their online prescribing system or consult the patient's psychiatrist, before prescribing Mysimba®. In group 2, all but one participant remembered the answer from the PPC, and the remaining participant selected the longest period (30 days) from the possible answers, since in his/her opinion, the longer the "washout" period, the safer it was to use Mysimba®. In practice, all said they would follow the 14-day washout recommendation.

In both groups, participants thought the survey question was clear, as well as the information in the PPC. None of the participants in group 1 recalled having seen any communication from the MAH on that issue, and one participant from group 2 thought the information would be in the SmPC. One participant in group 2 commented on the strange way the information was written in the PPC.

Concomitant Use of Mysimba® and Opioids

Several potential reasons for the observed concomitant use of Mysimba® and opioids were put forward and are listed below.

- Mysimba® and opioids were prescribed by two different physicians;
- The prescription system does not show a pop-up window to alert of the contraindication;
- Mysimba® or opioid was prescribed in paper format, making other physicians unaware of its use;
- The patient is not telling their physician (intentionally or not) about their opioid use, either because they do not use it regularly, they do not perceive it as a drug since they only use it for pain and not for a chronic disease, it was given to them by someone to reduce their pain, without them knowing it was an opioid, or they obtained opioids illegally.

In one participant's opinion, opioids are much more widely used in America, and concomitant use should not be a problem in Czech Republic. Another participant mentioned that opiates are monitored and the information should be in the patient's medication records, therefore a responsible physician would not prescribe it.

Recommendations from Czech Republic

Below is a list of recommendations for the PPC dissemination and for its content, based on participants' comments.

PPC dissemination

1. An online version of the PPC would be the preferred format.
2. If the paper format of the PPC is kept, the PPC should be distributed to physicians through a medical representative.

PPC content

1. The document title (i.e., Physician Prescribing Checklist) should be changed to a more meaningful title.
2. The list of contraindications and the list of factors that increase the risk of adverse reactions should be in the form of statements rather than questions.
3. The issues should be grouped by system organ class.
4. "Controlled hypertension" should be defined, and a list of drugs that would put patients at risk of adverse reactions when used concomitantly with Mysimba® should be provided.
5. The word "recent" in "recent myocardial infarction" is too vague and should be defined (e.g., within the last six months).
6. It should be specified if depression is treated or not.
7. Providing a list of antidepressants that can and cannot be combined with Mysimba® would help.
8. Some NB-452 survey questions on the PPC were badly translated in Czech and should be improved (question related to bupropion, controlled hypertension, myocardial infarction, and treatment with MAOI).

Summary of focus groups from Czech Republic

Participants found the PPC useful, well structured, and practical, and thought the information on conditions for use of Mysimba® was in general well summarized. However, some participants thought the PPC should be more concise. Participants agreed with the conditions for prescription discussed during the focus group. However, they proposed some adjustments in the PPC content, to avoid confusion. They also thought that the Czech translation of the PPC and the NB-452 survey questions should be improved. Some participants suggested to have an online version of the PPC available.
Some participants thought that having both mild and moderate hepatic impairment in the same survey question was confusing, and that their answer would be different for mild and moderate impairment. The current version of the PPC refers to moderate impairment only, which suggests an incoherence with the initial NB-452 survey question.

10.4.4. *Greece focus groups*

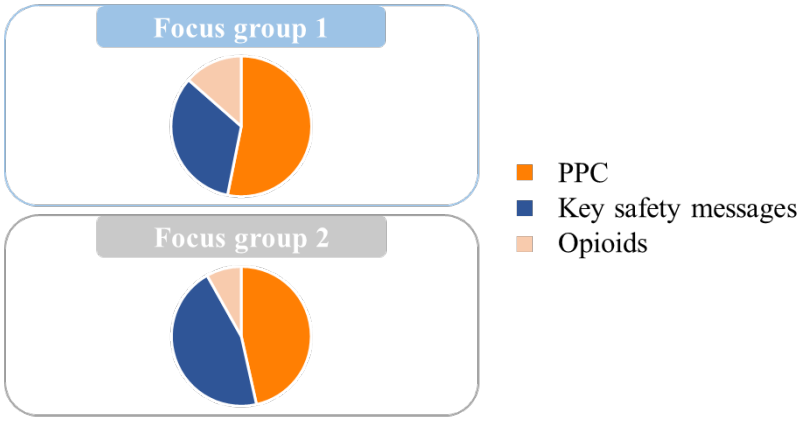
Themes discussed

The participants in both focus groups were particularly engaged and talkative. They made detailed statements with specific examples that often went beyond the questions.

Based on the coding of verbatims with QSR NVivo, the main themes addressed were the PPC in focus group 1, and both the PPC and key safety messages in focus group 2 (Figure 9). The most discussed key safety message in both focus groups was the increased risk of adverse events with depression (Figure 10). The estimated proportion of time spent on different topics for each key safety message is presented

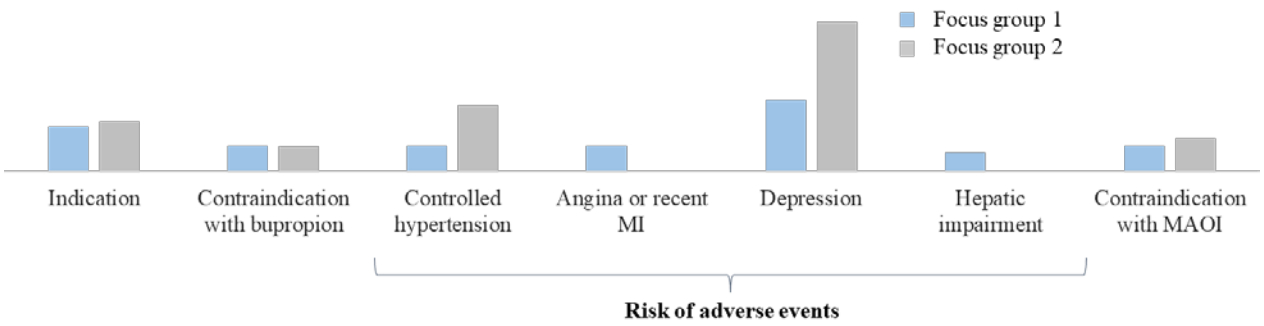
in Figure 14 in Document 2 of Annex 1.

Figure 9. Estimated proportion of time spent on themes for each focus group - Greece



PPC: Physician Prescribing Checklist

Figure 10. Estimated proportion of time spent on key safety messages for each focus group - Greece



MAOI: monoamine oxidase inhibitors, **MI**: myocardial infarction

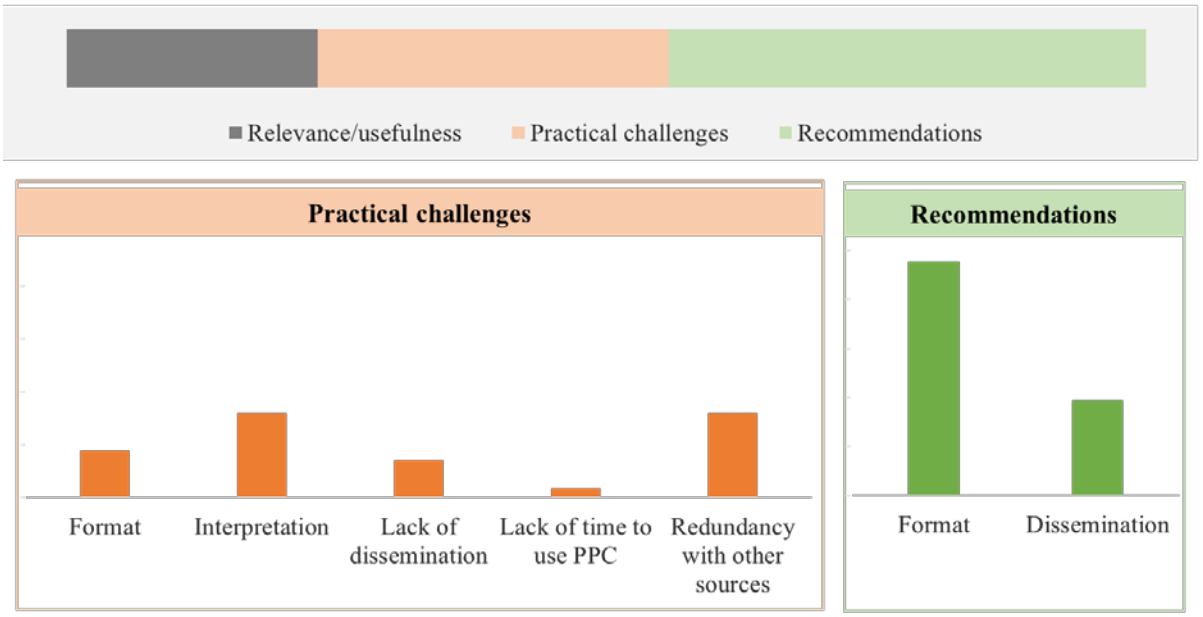
Physician Prescribing Checklist

Based on one participant's comments, the PPC was distributed to participants before the focus groups took place (*"I saw the prescriber's checklist when you [the moderator] sent it to me to participate in the research, never before."*). Apart from this participant, all had already seen or received the PPC before, mostly from a medical representative, except for one participant who found the PPC on his/her own on the internet. Most participants from both groups used the PPC when they had started prescribing Mysimba®, but no longer use it. However, one participant mentioned that he/she fills out the checklist for every patient and adds it in their file. Some participants of either group thought that the PPC should be in electronic format, rather than paper format, and that it was not necessary to fill out the list for each patient. One participant said that it did not make sense to ask physicians to fill out the PPC when patients could get Mysimba® directly from the pharmacy without a prescription. One mentioned the idea of having the PPC in a format that could be added to their electronic file, and also having a laminated card format to refer to when needed. Another participant thought that having an interactive list (e.g., when a contraindication is ticked, an "X" would appear on the screen) would be helpful.

When asked if they found the PPC useful, two participants from group 1 thought it would be useful for

GPs or physicians who have less knowledge of obesity. Another participant mentioned that it exaggerated on adverse events and that it could cause "prescription anxiety". This participant also did not understand why there was a checklist for Mysimba® but not for other drugs. Another participant from group 1 thought that GPs would be reluctant to prescribe Mysimba® because of the long checklist. Similarly, one participant from group 2 said that some physicians might be afraid to prescribe the drug, because they do not have all the necessary knowledge, especially in psychiatry. One participant mentioned that interaction with clopidogrel should be added as a risk, and another participant suggested to add a question on sleep apnoea, since it could cause uncontrolled hypertension.
The estimated proportion of time spent discussing PPC relevance/usefulness, practical challenges, and recommendations is presented in Figure 11 below.

Figure 11. Estimated proportion of time spent on PPC topics - Greece



Mysimba® Indication

One participant from each group mentioned that they did not have an opinion on the answer to the NB-452 survey question related to Mysimba® indication, since it was part of the indication. One participant from group 2 pointed out that "to < 30 kg/m^2" could be removed, since anyone who has a BMI over 27 and has comorbidities can receive Mysimba®, since those over 30 without comorbidities can already receive it. One participant from group 1 thought that the word "obese" should be replaced with "people with obesity" and others agreed.

Concomitant Use of Bupropion

On the question of concomitant use of Mysimba® and bupropion, most participants agreed with the answer. However, one participant from group 1 and two from group 2 suggested that bupropion be stopped, and Mysimba® started, since it would deal with obesity and depression together.

Medical Conditions with Increased Risk of Adverse Reactions

Below is a summary of participants' responses and comments on the third survey question related to medical conditions that could put patients at an increased risk of adverse reactions while taking Mysimba®.

Controlled hypertension

One participant from group 1 mentioned that, for a patient with controlled hypertension, Mysimba®, by helping the patient lose weight, could improve their hypertension. Another participant added that controlled hypertension was not an absolute contraindication. Participants from group 2 thought that "controlled" should be defined.

Angina or recent myocardial infarction

Very little time was spent on angina or recent myocardial infarction condition. In group 1, one participant said that, for a recent heart attack, Mysimba® was probably an absolute contraindication. The topic was not discussed in group 2.

Depression

One participant from group 1 thought that Mysimba® was relatively contraindicated for depression. Another participant mentioned that a psychiatrist should be consulted prior to prescribing any drug to a patient with depression. One participant from group 2 mentioned that Mysimba® could help a patient with untreated depression but could increase the risk of adverse reaction for a treated patient. This participant also mentioned that, for a mild depression, bupropion or Mysimba® and SSRIs could be used simultaneously, but for a major depression, a psychiatrist should be consulted prior to prescribing a drug. Two other participants from group 2 thought that avoiding prescribing Mysimba® to patients with treated depression could prevent them from benefiting from this drug.

Mild or moderate hepatic impairment

Very little time was spent on the mild or moderate hepatic impairment condition. In group 1, participants thought that Mysimba® was not an absolute contraindication for this condition. The topic has not been discussed in group 2.

Use of Monoamine Oxidase Inhibitor

Very little time was spent on concomitant use of Mysimba® and MAOI. All participants agreed with the survey answer, and one participant commented that MAOI was no longer used in Greece.

Concomitant Use of Mysimba® and Opioids

Potential reasons given by a participant from group 2 for the observed concomitant use of opioids and Mysimba® was the physician not informing their patients of the contraindication, and the possibility to buy opioids without a prescription in Greece. They mentioned that, to avoid concomitant use, physicians should ask for the list of all drugs the patient is taking or provide to the patient a list of drugs containing opioids. In group 1, one participant thought that the question on concomitant use was relevant for the

United States, where there is an opioid crisis, but not for Greece. Another participant from this group had a similar comment and mentioned that Greece had a rigorous framework for prescribing opioids. Another participant from group 1 also thought that the problem of concomitant use of opioids was irrelevant in Greece. Four participants from group 1 mentioned that patients with a chronic use of opioids were in general not overweight, or that their weight was not a priority.

Additional Risk Situation Identified

Based on participants' discussions, in Greece, Mysimba® can be purchased at the pharmacy without a prescription, which involves a risk of off-label use.

Recommendations from Greece

Below is a list of recommendations for the PPC dissemination and for its content, based on participants' comments.

PPC dissemination

1. The PPC should be available in Greek (unclear as to which format the comment applied to – paper or electronic).
2. The PPC could be in a format that would allow physicians to add it to their patient electronic file.
3. A laminated card format would be useful, to quickly refer to when needed.
4. An interactive checklist would be helpful (e.g., when a contraindication is ticked, an "X" would appear on the screen).
5. Paper format should be kept, as some physicians use it.

PPC content

1. Interaction with clopidogrel should be added.
2. The "to < 30 kg/m^2" could be removed from the indication since it is redundant with "> 30 kg/m^2".
3. The term "people with obesity" should be used instead of "obese".
4. Controlled hypertension should be defined.
5. It should be specified if depression is treated or not.

Summary of focus groups from Greece

Conversations in both focus groups went into different directions beyond the objectives of the study. Nevertheless, all participants agreed that some adjustments needed to be made to the PPC to provide more clarity to physicians using it. According to participants, the PPC is a useful tool, especially for GPs, and was mainly used by participants when Mysimba® was new on the market.

10.5. Other analyses

Not applicable.

10.6. Adverse events/adverse reactions

Not applicable.

11. Discussion

11.1. Key results

Focus groups' discussions are summarised below in relation to the three *a priori* hypotheses that were put forward as potential root causes of lack of knowledge about the existence of the PPC (section 7).

1. *Prescribers are aware of the checklist, but the term "PPC" is not used by clinicians in their routine clinical practice setting.*

Several focus group participants knew what the PPC was, although some thought the name did not mean anything, and suggested to have a more meaningful name. Therefore, this hypothesis is confirmed.

2. *Clinicians remember the PPC, but dissemination occurred too long ago, and they forgot about its existence.*

Some participants remembered the PPC from the time dissemination occurred (when Mysimba® was new on the market). A few participants received the PPC from a medical sales representative, but not recently. This points to hypothesis being confirmed and suggests that mode and timing of dissemination may be an issue. It is also possible that those clinicians who remember the PPC when it was first distributed, no longer use it, because they believe it is no longer useful to fill in for every patient, which is consistent with some confusion about the purpose of the PPC that was raised during focus group sessions. Availability in an electronic format and modification of the title to clarify its purpose were suggested by participants to enhance usage.

3. Clinicians did not see the PPC (i.e., inadequate mode of dissemination) In each country, one or two participants claimed they had never seen the PPC. A potential reason for not having seen the PPC could be the difficulty for medical representatives to meet some physicians and in Norway, not being visible in the *Felleskatalogen*.

Potential *a priori* root causes of incorrect answers to the survey regarding key safety messages included the following:

1. *Lack of use of the PPC (i.e., problem of implementation of aRMM).*

In Norway, none of the participants used the PPC, because they did not see it on the *Felleskatalogen* website (even though it has been posted on the website, it is not easy to find). They do, however, rely on *Felleskatalogen* as a source of information.
However, all participants from Czech Republic who had received the PPC (all but one of the Czech participants had received PPC), and most participants from Greece, had used the PPC when Mysimba®

was new on the market, but no longer use it. Although the PPC dissemination plan varied across countries (i.e., posted on a website in Norway and paper format distributed through sales representatives in Greece and Czech Republic), lack of recent use appears to be a common observation.

2. Incorrect processing of information (i.e., problem with understanding the key safety messages).

The questions on medical conditions that could increase the risk of adverse reactions were not well understood by several participants, who confused contraindication and increased risk of adverse effect. For example, all participants from group 1 in Norway thought that Mysimba® could not increase the risk of adverse reactions when hypertension was controlled, since the latter was part of the approved indications for Mysimba®. Most participants from both groups also said that Mysimba® was contraindicated for angina or recent myocardial infarction. In Czech Republic, for the recent myocardial infarction condition, participants thought that the word "recent" was too vague, and that a period of time (e.g., within the last six months) since myocardial infarction occurred should be defined. Participants from Greece correctly responded that Mysimba® was not an absolute contraindication for controlled hypertension, was relatively contraindicated for depression, and was probably an absolute contraindication for a recent heart attack. Further clarification on these key safety messages would appear warranted although they need to be aligned with the SmPC.
Regarding depression, focus group participants do not seem to recognize the increased risk of AE in patients treated with Mysimba® and had different opinions depending on whether depression was treated or not. For untreated depression, some consider that Mysimba® may actually alleviate depressive symptoms.

3. Conflicting sources of information (i.e., clinicians may have been exposed to sources of information other than the SmPC or the PPC, which may not explicitly cover the key safety messages).

In Norway, participants pointed out that in order to get a blue prescription for Mysimba® (i.e., a prescription for a medicine fully or partly funded by the State), the criteria were much more restrictive than those stated in the PPC. One participant mentioned that he/she would have therefore given a different answer for Mysimba® indication than those provided in the answer choices. Another participant asked for clarification as to whether the survey question was related to the criteria for a blue prescription, which indicates an ambiguity in Norway regarding the approved indication.

4. Inadequate formulation of the questions in the survey (i.e., problem with the evaluation method).

For the question on whether mild or moderate hepatic impairment could increase the risk of adverse events, participants had different answers for each severity. It was noted by some participants that the PPC indicated only the moderate severity. This suggests an incoherence between the PPC (which only refers to moderate impairment) and the initial NB-452 survey question (which referred to both mild and moderate). Inadequate understanding of the safety message on hepatic impairment observed in the NB-452 survey was thus likely due to an inadequate survey question rather than poor PPC comprehension.

11.2. Limitations

Participant bias: Participants may respond to the questions based on what he/she thinks is the right answer or according to social acceptability or to agree with the moderator. Questions in the focus groups were open-ended in order to avoid participant from simply agreeing or disagreeing with the moderator and were not able to use a simple "yes" or "no" answer. In order to minimize social desirability or observer bias, questions were phrased in a manner to allow the participant to feel accepted, regardless of his/her answer or KAU.

Selection bias: Owing to data privacy regulations, it was not possible to target participants in the initial NB-452 KAU survey. A purposeful sample of prescribers was used for this qualitative study, and none of the focus group respondents had participated in the KAU survey;however, all were presented with the survey questions that were less well understood in the survey and were not shown the answers right away. Although a maximum variation purposive sample was initially sought, only GPs participated in the focus groups in Norway, which corresponds to the majority of participants in the initial NB-452 survey. In addition, some were from the same office, which likely reduces the variation in comments and opinions originating from this country.

Researcher bias: May occur if a researcher interprets the data to support his/her hypothesis. There was no *a priori* hypothesis communicated to the moderator, and data were analysed independently by someone not involved in the interviews. Questions were kept simple, and no leading questions were used that could prompt participants to respond in favour of a particular assumption.

11.3. Interpretation

Based on the focus groups, issues related to PPC implementation are likely the main reason for lack of awareness of some key safety messages. Although not all focus group suggestions can or should be implemented, below are the recommendations made by the focus group participants to improve the distribution and usefulness of the PPC:

- Make a list of statements instead of questions
- Improve conciseness
- Group issues by system organ class
- Improve title to highlight the PPC objectives (e.g., "Checklist before treatment commence" or "Checklist prior to treatment")

- Participants also recommended that a new round of dissemination would be relevant in all countries where Mysimba® is marketed, by a medical representative, and as an electronic form for daily use *(to be discussed with local distribution partners before possible implementation)*
- Improve translation into local languages, including cultural adaptation *(to be discussed)*
- Specifically for Norway, position the PPC in a more visible location in *Felleskatalogen (to be discussed)*

The following recommendations on the content of the PPC were made by participants in order to improve the understanding of key safety messages. However, these were deemed not feasible within the EU regulatory context:

- Integrate the PPC into the prescription system and/or medical records system
- Create an interactive electronic version, where a pop-up message would appear when a contraindication or risk of adverse reaction is selected
- Have the PPC in a concise card format
- Include operational definitions for controlled and uncontrolled hypertension, depression, and recent myocardial infarction. By adding definitions, the PPC would no longer be consistent with the Summary of Product Characteristics (SmPC)
- List contraindicated drugs, including brand names; however, *brand names are country-specific and not easily incorporated into the RMM*
- Inform on interaction with clopidogrel - Drugs within a class cannot be singled out

11.4. Generalisability

Qualitative research does not aim at statistical generalization.

12. Other information

Not applicable.

13. Conclusion

Based on outputs of the focus groups, the MAH plans to reformat the PPC by modifying the title with a clarification on the purpose of the PPC and phrasing safety messages as statements instead of questions, with grouping by themes. Other recommendations emerging from the focus groups regarding content, such as adding definitions and brand names, are not considered feasible in order to maintain alignment with the Mysimba SmPC. It is planned to disseminate the updated (reformatted) PPC at the next opportunity agreed with EMA, once approved by EMA and national competent authorities, in each country where Mysimba® is launched. The MAH will also interact with national distribution partners to assess the feasibility of providing electronic distribution in each of these countries.

These findings and resulting modifications of the aRMM will likely contribute to the appropriate use of Mysimba® and to maintaining the positive benefit-risk balance of the product.

14. References

[1] EMA, "Guideline on good pharmacovigilance practices (GVP) - Module VIII - Post-authorisation safety studies (Rev 3)," 9 October 2017. [Online]. Available: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-viii-post-authorisation-safety-studies-rev-3_en.pdf. [Accessed 1 June 2022].

[2] The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), "Guide on Methodological Standards in Pharmacoepidemiology (Revision 10)," 30 June 2022. [Online]. Available: http://www.encepp.eu/standards_and_guidance. [Accessed 19 July 2022].

[3] CIOMS, "International Ethical Guidelines for Health-related Research Involving Humans," 2016. [Online]. Available: https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf. [Accessed 1 June 2022].

[4] H. I. B. T. R. D. C. D. O'Brien BC, "Standards for Reporting Qualitative Research - A Synthesis of Recommendations," *Academic Medicine,* vol. 89, no. 9, pp. 1245-1251, 2014.

[5] H. J. B. L. e. a. Walsh I, "What Grounded Theory Is...A Critically Reflective Conversation Among Scholars," *Organizational Research Methods,* vol. 18, no. 4, pp. 581-599, 2015.

[6] C. V. Braun V, "Using thematic analysis in psychology," *Qualitative Research in Psychology,* vol. 3, no. 2, pp. 77-101, 2006.

[7] S. P. C. J. Tong A, "Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups," vol. 6, pp. 349-57, 1 December 2007.

[8] P. MQ, Qualitative research and evaluation methods, Thousand Oaks, California: 3rd Sage Publications, 2002.

[9] H. S. G. C. e. a. Palinkas LA, "Purposeful sampling for qualitative data collection and analysis in mixed method implementation research," *Adm Policy Ment Health,* vol. 42, no. 5, pp. 533-544, 2015.

[10] D. W, "What about focus group interaction data?," *Qual Health Res,* vol. 15, no. 6, pp. 832-40, 2005.

[11] T. L. J. C. e. a. Dos Santos Marques IC, "Implementation of virtual focus groups for qualitative data collection in a global pandemic," *Am J Surg,* vol. 221, no. 5, pp. 918-922, 2021.

[12] B. M. D. G. Matthews KL, "Using Online Meeting Software to Facilitate Geographically Dispersed Focus Groups for Health Workforce Research," *Qual Health Res,* vol. 28, no. 10, pp. 1621-1628, 2018.

[13] E. L. N. J. J. A. L. C. Wettergreen L, "Online Focus Group Discussion is a Valid and Feasible Mode When Investigating Sensitive Topics Among Young Persons With a Cancer Experience," *JMIR Res Protoc,* vol. 5, no. 2, p. e86, 2016.

[14] M. DL, Focus groups as qualitative research, 2nd Edition ed., Thousand Oaks, California: Sage, 1997.

[15] K. RA, Focus groups: A practical guide for applied research, 2nd Edition ed., Thousand Oaks, California: Sage, 1994.

Appendices

Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1		*23 OCT 23*	*PPC before Treatment with Mysimba*
2		*23 OCT 23*	*Modifications made for a reformatted PPC*

Annex 2. Additional information

N/A