30 May 2024
EMA/CHMP/236208/2024

CHMP List of questions

To be addressed by the marketing authorisation holder for Mysimba

Procedure under Article 20 of Regulation (EC) No 726/2004

Mysimba - EMEA/H/A-20/1530/C/003687/0065

Marketing authorisation holder: Orexigen Therapeutics Ireland Limited

INN/active substance: Naltrexone hydrochloride/Bupropion hydrochloride

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The marketing authorisation holder (MAH) is requested to address the following questions:

Question 1

Please provide information on the estimated patient exposure to naltrexone/bupropion in the different European Economic Area Member States and worldwide. This should include a line listing/detail of data from ongoing and completed clinical studies, non-interventional studies and post-marketing sources; presented separately.

Data on the use in clinical practice including information on dose, duration of treatment and reasons for discontinuation should be provided, if available.

Question 2

The MAH is asked to submit all available data from (interventional and non-interventional) clinical studies with Mysimba concerning cardiovascular safety as well as data on blood pressure and heart rate measurements (overall and separately by duration of treatment and for the groups of early responders (≥ 5% weight loss at week 16), and non-responders) in the approved indication for Mysimba. This should include previously submitted data and any new data that were not submitted yet, e.g. from other (ongoing) clinical studies MAH-sponsored or not. A comprehensive summary and critical discussion of these data should be provided, with a special focus on long-term cardiovascular safety.

Question 3

Please provide a cumulative review of all spontaneous and solicited case reports of first MACE, MACE and other cardiovascular adverse events reported with Mysimba as a suspected or interacting medicinal product received from the MAH's safety database, literature and other available databases, e.g. EudraVigilance.

Question 4

The MAH is requested to provide a complete study protocol, including the statistical analysis plan (SAP), of a cardiovascular outcome (CVOT) study adequately designed to generate robust evidence on the long-term cardiovascular safety of Mysimba. Any differences to previously submitted study protocols and the NB-CVOT LIGHT study should be highlighted and the rationale for changes should be provided. Specify how many patients are expected to take Mysimba for which period of time during the study, in order to explain to which extent, the study will be able to generate data further to long-term treatment. Specify a success criterion which would ensure the long-term safety and adequate analysis methods in case of non-proportional hazards. Furthermore, timelines for milestones (e.g. recruitment, results) should be indicated.

Question 5

The MAH is asked to submit all available data in support of a therapeutic benefit of Mysimba in its approved indication with respect to long-term clinical benefits, e.g. beyond 1 year. This should include any data that were not submitted at the time of the initial marketing authorisation, e.g. from (ongoing) clinical studies or published literature. A comprehensive summary and critical discussion of these data should be provided. For RCTs, e.g. the NB-CVOT LIGHT study, the results of the efficacy analyses should be provided using all randomised patients with a treatment policy strategy for treatment discontinuation and reference based multiple imputation for missing data. The amount of intercurrent events such as treatment discontinuation, dose interruptions/reductions and concomitant medication should be adequately described per treatment arm per study. In addition, to facilitate a comparison between the studies, the same imputation methods as for

studies that supported the initial marketing authorisation should be applied for results from these studies.

Question 6

Provide a full benefit-risk balance evaluation of Mysimba in the currently approved indication(s), including a clear overview of all available efficacy and safety data (i.e. previously submitted and new data including short-, intermediate- and long-term data). In particular, the benefit-risk balance for long-term use should be discussed considering the uncertainties with respect to long-term CV safety.

Question 7

Provide justified proposals for any (additional) risk minimisation measures, including changes to the summary of product characteristics and package leaflet, addressing remaining risks and/or uncertainties in relation to treatment with Mysimba in its approved indication. For any proposed risk minimisation measures a critical discussion of the feasibility and expected effectiveness of those measures in clinical practice should be provided. Activities to measure the effectiveness of such measures should also be proposed.