Annex IV

Scientific conclusions

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Mysimba is a centrally authorised product containing a fixed-dose combination of naltrexone and bupropion. The exact neurochemical appetite suppressant effects of naltrexone and bupropion are not fully understood. Naltrexone is a mu-opioid antagonist and bupropion is a weak inhibitor of neuronal dopamine and norepinephrine reuptake. These components affect two principal areas of the brain, specifically the arcuate nucleus of the hypothalamus and the mesolimbic dopaminergic reward system.

Mysimba is indicated as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients (≥18 years) with an initial body mass index (BMI) of:

- ≥ 30 kg/m^2 (obese), or
- ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of one or more weight-related co-morbidities (e.g., type 2 diabetes, dyslipidaemia, or controlled hypertension)

Treatment with Mysimba should be discontinued after 16 weeks if patients have not lost at least 5% of their initial body weight. The need for continued treatment should be re-evaluated annually.

The product was granted a marketing authorisation in March 2015 based on results from four multicentre, double-blind, placebo-controlled obesity phase 3 studies (NB-301, NB-302, NB-303 and NB-304), demonstrating superiority of naltrexone/bupropion to placebo for the two co-primary endpoints (i.e. percent change from baseline body weight and the proportion of subjects achieving ≥5% total decreased body weight) measured at week 56 (NB-301, NB-302, and NB-304) or week 28 (NB-303). At the time of the marketing authorisation application (MAA) evaluation, there were uncertainties regarding the true size of the effect given the high drop-out rate (around 50%), and the use of an imputation method for missing data which could have overestimated the treatment effect. However, when viewing the results of the primary endpoints as well as the secondary glycaemic and lipid-related endpoints in totality, the efficacy was considered to be clinically relevant.

In the phase 3 programme, naltrexone/bupropion was associated with transient relative mean increases in blood pressure (BP) (~1-2 mmHg) and in heart rate (~1.5 bpm) compared to placebo. Tachycardia was more commonly reported with naltrexone/bupropion than with placebo. In addition, myocardial infarction occurred more frequently in the naltrexone/bupropion group than in the placebo group, albeit the numbers were very small. In clinical practice, cases of hypertension have been reported with other bupropion-containing products, including some severe cases requiring acute treatment. It was further noted that post-marketing cases of hypertensive crisis had been reported during the initial titration phase with naltrexone/bupropion, and hypertensive crisis was identified as an adverse reaction in 2020.

During the assessment of the MAA, a cardiovascular outcome trial (NB-CVOT; also referred to as the LIGHT trial) was ongoing and the first interim report of the study was submitted. The objective of the NB-CVOT study was to assess the occurrence of major adverse cardiovascular events (MACE) in overweight and obese patients with CV risk factors receiving Mysimba. The primary analysis of the intent-to-treat (ITT) population showed that statistically significantly more subjects treated with placebo (59 subjects, 1.3%) compared to naltrexone/bupropion (35 subjects, 0.8%) experienced MACE (hazard ratio [HR] [95%CI] 0.59 [0.39-0.90]).

Although these interim results were reassuring in the short and intermediate term, uncertainty remained with respect to long-term CV safety given the limited exposure time in the study (~30 weeks) and the effects of naltrexone/bupropion on BP. Therefore, in order to further investigate the long-term CV safety of naltrexone/bupropion, the conduct of a multicentre, randomised, double-blind, placebo-controlled, phase 4 study to assess the effect of naltrexone/bupropion on the occurrence of MACE in overweight and obese subjects was requested by the Committee for Medicinal Products for Human Use (CHMP) and imposed as a condition to the marketing authorisation. The results were due to be submitted by end of March 2022. However, this first NB-CVOT was terminated prematurely due to preterm unblinding.

A second CVOT study (NB-CVOT-2, also called NB-4001, or CONVENE) was initiated but also prematurely terminated in 2016. At that time, a third CVOT (NB-CVOT-3) was to be initiated to comply with

the condition to the marketing authorisation. Annual progress reports were requested, but in November 2019, the NB-CVOT-3 study had still not been initiated.

In December 2020, based on data from the United States (US) showing that the majority (approximately 80%) of patients discontinued treatment with Mysimba prior to the stopping rule at 4 months, the marketing authorisation holder (MAH) claimed that the CVOT study, planned to be conducted in the US, was no longer feasible in its original design. Therefore, in 2021, the MAH proposed an alternative protocol: a health outcome study, designed as a retrospective database cohort study using electronic health records as primary data source (EMEA/H/C/003687/ANX/001.6). This study design was not endorsed by the CHMP and its Scientific Advice Working Party (SAWP), as it was considered that this study would not provide relevant data regarding the long-term CV safety as required when the marketing authorisation of Mysimba was granted.

In January 2022, in the context of variation application EMEA/H/C/003687/II/0056, the MAH proposed another alternative protocol to replace the planned imposed CVOT study: a randomised, placebo-controlled, double-blind phase 4 pragmatic trial, intended to capture CV outcomes during the real-world use of naltrexone/bupropion after initial randomisation in order to assess the effect of naltrexone/bupropion on the occurrence of MACE in overweight and obese subjects with documented CV disease. The results of this study were not expected before 2027. During the variation procedure, the CHMP raised a number of concerns with the study design of this alternative study proposal, in particular with the sample size, the statistical methods and the milestone timelines. The protocol reviewed by CHMP was not considered acceptable since these concerns were not addressed. Overall, the CHMP, taking into account the view of the Pharmacovigilance Risk Assessment Committee (PRAC), did not consider the proposed alternative study sufficient to generate robust evidence on the long-term CV safety of Mysimba. Additional risk minimisation measures proposed by the MAH were also considered insufficient to mitigate the potential CV risk for patients receiving long-term treatment and to overcome the need for a study investigating long-term CV safety.

In July 2023, in view of the remaining concern regarding the potential long-term CV safety risk of Mysimba, and the lack of adequate study plan to address the uncertainty about this risk, the CHMP considered that a review of all available data on this risk and its impact on the benefit-risk balance of Mysimba in its approved indication needed to be conducted. On 1 September 2023, the EC triggered a procedure under Article 20 of Regulation (EC) No 726/2004, and requested the CHMP to assess the impact of the above concerns on the benefit-risk balance of Mysimba and issue a recommendation on whether the marketing authorisation should be maintained, varied, suspended or revoked.

Overall summary of the scientific evaluation

The CHMP considered the data submitted by the MAH in relation to the long-term CV safety and efficacy of Mysimba in its authorised indication. This included data from the pivotal clinical trials, additional post hoc analysis, data from the early-terminated NB-CVOT-1 trial as well as data from non-interventional studies, literature, and post-marketing safety reports.

Regarding the efficacy, despite the more modest treatment differences between Mysimba and placebo observed in the post hoc analysis of the pivotal phase 3 studies compared with the original analyses, the weight change from baseline, as well as the ≥5% and ≥10% weight loss responder analyses, were all in favour of Mysimba. The results indicated a statistically significant reduction of body weight compared to placebo after approximately 1 year of treatment. In comparison, the treatment effect at week 52 in the ITT analysis of the NB-CVOT-1 study was somewhat lower compared to the results of the pivotal phase 3 trials. However, in this study, compared to placebo, the proportion of subjects with ≥5% weight loss from baseline and the proportion of subjects with ≥10% weight loss from baseline was declining beyond 1 year. Still, the results do not question the effect observed in the phase 3 studies leading to the authorisation of Mysimba and the conclusions that the efficacy of Mysimba in weight management is limited but considered to be clinically relevant. Beyond 1 year of treatment with Mysimba, limited clinical data are available. In the NB-CVOT-1 study, the mean differences in weight loss in the PP population at 52, 104, and 208 weeks were -3.66 kg (95% CI [-4.15, -3.17]), -3.16 kg (95% CI [-3.82, -2.49]), and -3.03 kg (95% CI [-3.87, -2.19]), respectively.

However, for the ITT population, using an appropriate imputation method (reference-based multiple Imputation or Baseline Observation Carried Forward (BOCF)), these values are expected to be lower. The CHMP further noted that the results from the NB-CVOT-1 study should be interpreted with caution due to its early termination. This may have impacted the robustness and reliability of the findings. In addition, this study was not designed to assess long-term efficacy on the reduction in body weight as either a primary or secondary endpoint.

Regarding safety, the reviewed pooled data of the phase 3 studies confirmed the safety outcomes reported in the initial marketing authorisation application for Mysimba. In these analyses, Mysimba was associated with less pronounced reductions in BP and heart rate compared to placebo. Over 1 year, the HR point estimates for MACE in the NB-CVOT-1 study suggested a trend towards a reduced risk for MACE, but the extent of this reduction decreased over time (HR 0.61, 95% confidence interval [CI], [0.2-1.29], 0.62, 95% CI, [0.39-0.98] and 0.73, 95% CI [0.47-1.14]) at ≤16 weeks, 16-52 weeks, and 52-104 weeks, respectively). In addition, the differences observed between the placebo and active treatment groups in this study for BP and heart rate were minimal. However, the information for patients receiving treatment beyond 1 year of treatment in this study was very scarce due to the high number of treatment discontinuations.

Additional data from non-interventional studies, literature and post-marketing reports do not add a concern in relation to the CV risk. The completed health outcomes analysis identified no evidence of excess CV risk and no statistically significant difference in MACE between Mysimba and the comparator group (lorcaserin). In another real-world study, the DUS NB-451, CV event were not common in patients receiving Mysimba. From the literature review and published meta-analysis, it seemed that Mysimba does not appear to significantly increase the risk of major CV events compared to other treatments. Further, the rate of events gathered from post-marketing safety reports did not raise a significant concern with the CV safety of Mysimba. The CHMP however noted that, while reassuring, this type of data brings limited value due to its inherent limitations. Consequently, it cannot alleviate the uncertainty related to long-term CV safety of Mysimba.

Hence, the CHMP considers that the CV safety concern, which was raised because of findings of unfavourable BP changes and increased heart rate at time of the marketing authorisation of Mysimba, remains. Additionally, the data reviewed do not allow CHMP to conclude on the long-term CV safety of Mysimba and the uncertainty identified at the time of the marketing authorisation remains. Therefore, the uncertainties regarding long-term CV safety beyond 1 year of treatment still need to be addressed with data coming from a CVOT, as per the condition to the marketing authorisation.

In order to comply with the condition to the marketing authorisation and address the uncertainties in relation to the long-term CV risk, the MAH should submit the results of the NB-CVOT-3 (INFORMUS) study. The study is ongoing, and as of 31 January 2025, 2,825 patients had been randomised. The CHMP considered the study acceptable, with some protocol amendments, as a replacement of the CVOT study currently imposed as a condition to the marketing authorisation (category 1 study). The following amendments were introduced in the protocol: inclusion of an expanded MACE endpoint as a new secondary endpoint (i.e., MACE or any coronary, cerebrovascular and peripheral revascularization events, or hospitalization for heart failure), other additional endpoints (all-cause death and time to all-cause death), sensitivity analyses to mitigate potential misclassification of events, additional analysis to address competing risks, as well as new analyses to strengthen the understanding of the treatment effect under various scenarios (e.g. different intercurrent event strategies for treatment discontinuation and death, informative censoring due to loss of follow-up and different analysis priors). The study results should be submitted by 31 December 2028. Additionally, the MAH should submit annual reports on the study progress. This is to be reflected in the RMP accordingly.

To note, while the Bayesian approach to be followed in the study was accepted, the CHMP considers that the frequentist approach is of equally importance and should lead to similar conclusions. In addition, sensitivity analyses using weakly and non-informative priors are essential to contextualise the study results and should be provided by the MAH with the study results. Therefore, if not provided by the MAH, these analyses and simulations concerning the frequentist operating characteristics for the Bayesian analyses will be requested when the study results are available.

Importantly, the CHMP emphasised that the study results will not be evaluated simply based on its primary non-inferiority test. The magnitude and precision of the risk estimates in the study will be assessed against the totality of data generated in the study and in the context of all available evidence on the CV safety of Mysimba. Remaining uncertainty in the study results, related to poor precision of estimated risks, insufficient follow-up, or concerns regarding remaining bias, will be considered in the overall assessment and may adversely impact the benefit-risk balance of Mysimba.

Further, while the CVOT-3 study results are not available and the uncertainty regarding the long-term CV risk remains, the CHMP considered that only patients who benefit from long-term treatment should continue treatment with Mysimba for longer than 1 year, considering the potential long-term CV risk of Mysimba. As a consequence, the CHMP recommends that treatment with Mysimba beyond 1 year should be discontinued if the efficacy success criteria already established for the product after 16 weeks of treatment is not at least maintained. Namely, treatment with Mysimba should be discontinued if patients, after one year of treatment, have not maintained a loss of at least 5% of their body weight. Additionally, it should be specified in the product information that the CV risks of Mysimba when given for longer than a year have not been fully determined. Further, when annually assessing the treatment continuation, healthcare professionals (HCPs) should monitor the absence of adverse change in patients' cardiovascular risk and maintenance of weight loss of at least 5% of their initial weight. This assessment should be conducted in discussion with the patient (SmPC section 4.2). With these measures, only patients sustainably benefiting from treatment will be exposed to Mysimba for more than 1 year, thereby minimising potential long-term CV risks for those who do not benefit from it. In order to adequately inform HCPs of these measures and ensure appropriate use of Mysimba, the existent prescriber guide (named 'physician prescribing checklist') should be updated to reflect this recommendation. A direct healthcare professional communication (DHPC) is also to be distributed. Additionally, the available educational materials to be used by HCPs when discussing the treatment with patients should be reflected in the product information (SmPC section 4.4).

In view of the above, the Committee considers that the benefit-risk balance of Mysimba remains favourable subject to the agreed condition to the marketing authorisation, and taking into account the agreed amendments to the product information and other risk minimisation measures.

CHMP opinion

Whereas

- The CHMP considered the procedure under Article 20 of Regulation (EC) No 726/2004 for Mysimba.
- The CHMP reviewed all available data submitted by the MAH in relation to the long-term cardiovascular safety and the efficacy of Mysimba in its authorised indication. This included data from the pivotal clinical trials, additional post-hoc analysis, data from the early-terminated CVOT-1 trial as well as data from non-interventional studies, literature and post-marketing safety reports. In addition, the CHMP considered a new CVOT study protocol, proposed by the MAH in order to further characterise the long-term cardiovascular safety and to fulfil the Annex II.D condition to the marketing authorisation.
- The CHMP considers that the available data remain insufficient to address the concern already identified at the time of the marketing authorisation regarding the long-term cardiovascular safety.
- While this uncertainty remains, the CHMP considers that treatment with Mysimba should be discontinued after one year if a patient has not maintained a loss of at least 5% of their initial body weight. Further, when annually assessing the treatment continuation, healthcare professionals should monitor the absence of adverse change in patients' cardiovascular risk and maintenance of weight loss of at least 5% of their initial weight. This assessment should be conducted in discussion with the patient.
- Finally, the CHMP considers that the ongoing cardiovascular safety study (INFORMUS) , as per its further amended protocol, is appropriate to generate evidence on the long-term cardiovascular safety of Mysimba. Additional relevant analyses not reflected in the protocol will be requested when the study results are available, if necessary. Overall, the study is considered acceptable as replacement of the CVOT study that is currently imposed as a condition to the marketing authorisation.

The Committee, as a consequence, concluded that the benefit-risk balance of Mysimba is favourable subject to the agreed condition to the marketing authorisation, and taking into account the agreed amendments to the product information and other risk minimisation measures.