NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 20 OF REGULATION (EC) 726/2004

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This notification is a referral under Article 20 of Regulation (EC) 726/2004 to the Committee for Human Medicinal Products (CHMP) made by the European Commission (EC):

Product(s) Name(s)	Mysimba
Active substance(s)	naltrexone / bupropion
Pharmaceutical form(s)	All
Strength(s)	All
Route(s) of Administration	All
Marketing Authorisation Holder(s)	Orexigen Therapeutics Ireland Limited

Background

Mysimba is a prolonged-release tablet containing a fixed dose combination of naltrexone and bupropion. The exact neurochemical appetite suppressant effects of naltrexone/bupropion are not fully understood. The medicinal product has two active substances: naltrexone, a mu-opioid antagonist, and bupropion, a weak inhibitor of neuronal dopamine and norepinephrine reuptake. These active substances affect two principal areas of the brain, specifically the arcuate nucleus of the hypothalamus and the mesolimbic dopaminergic reward system.

Mysimba is a centrally authorised product 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 product was granted a marketing authorisation (MA) in March 2015 based on results from four multicentre, double-blind, placebo-controlled obesity Phase 3 studies (naltrexone extended release (ER) /bupropion ER (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 time of the MA evaluation, there was uncertainty 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 overestimate the treatment effect.

In the Phase 3 programme, naltrexone/bupropion was associated with transient relative mean increases in blood pressure (~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 numbers were very small. In clinical practice with other

bupropion containing products, hypertension, in some cases severe and requiring acute treatment, has been reported.

Although interim results of a cardiovascular outcome trial (NB-cardiovascular outcome trial (CVOT), also LIGHT trial) were reassuring in this regard in the short and intermediate-term, uncertainty remained with respect to long-term cardiovascular safety given the limited exposure time in the study (~30 weeks) and the effects of naltrexone/bupropion on blood pressure. Therefore, in order to further investigate the long-term cardiovascular 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 major adverse cardiovascular events (MACE) in overweight and obese subjects was imposed as condition to the MA (CVOT-2; Annex IID condition; results due by end of March 2022).

After the MA, still in 2015, the NB-CVOT was terminated prematurely due to preterm unblinding. A second CVOT study (CVOT-2, also NaltrexBuprop-4001, or CONVENE) was initiated but also prematurely terminated in 2016. At that time, a third CVOT (CVOT-3) was to be initiated to comply with the condition to the MA. Annual progress reports were requested but in November 2019 it was evident, that the third CVOT study had still not been initiated.

Issues to be considered

In December 2020, based on US data 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 the CVOT, 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 (EHR) as primary data source (EMEA/H/C/003687/ANX/001.6). The study design was not endorsed by the CHMP and its Scientific Advice Working Party (SAWP), as it was considered that this study would not be able to provide relevant data regarding the long-term cardiovascular safety as required.

In January 2022, in the context of variation application EMEA/H/C/003687/II/0056, the MAH proposed the synopsis of another alternative protocol to replace the planned imposed CVOT study: a randomised, placebo-controlled, double-blind Phase 4 pragmatic trial, intended to capture cardiovascular 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 cardiovascular (CV) disease. Results would not be expected to be available before 2027. The CHMP, taking into account the view of the Pharmacovigilance Risk Assessment Committee (PRAC), also did not consider the alternative proposed by the MAH sufficient to generate robust evidence on the long-term cardiovascular safety of Mysimba. Additional risk minimisation measures proposed by the MAH were considered insufficient at this stage to mitigate the potential cardiovascular risk for patients receiving long-term treatment and to overcome the need for a study investigating long-term cardiovascular safety.

It is further noted that post-marketing cases of hypertensive crisis have been reported during the initial titration phase with naltrexone/bupropion, based on which hypertensive crisis was identified as an adverse reaction in 2020.

In view of the remaining concern regarding the potential long-term cardiovascular safety risk of Mysimba, and the lack of adequate study plan to address the uncertainty about this risk, the CHMP considered in July 2023, as an outcome of the aforementioned variation, that a review of all available data on this risk and its impact on the benefit-risk balance of Mysimba in its approved indication should be conducted.

In view of the above, the EC initiates a procedure under Article 20 of Regulation (EC) No 726/2004 and requests the Agency/CHMP to assess the above concerns and their impact on the benefit risk balance for the centrally authorised medicinal product(s) Mysimba (naltrexone/bupropion), taking into account any consequences from the failure to comply with the obligations laid down in the marketing authorisation. The EC requests the Agency/CHMP to give its opinion by 31 May 2024 on whether the marketing authorisation for this/these products should be maintained, varied, suspended or revoked.

In addition, the EC requests the Agency/CHMP to give its opinion, as soon as possible, as to whether temporary measures are necessary to ensure the safe and effective use of this medicinal product, taking into account any consequences from the failure to comply with the obligations laid down in the marketing authorisation.

Signed Date
Olga Solomon
Head of Unit - Medicines: policy, authorisation and monitoring
Health and Food Safety Directorate General