29 May 2025

Mysimba (naltrexone/bupropion): long-term cardiovascular risk and new recommendations on annual assessment

Dear Healthcare professional,

Orexigen Therapeutics Ireland Limited (OTIL) in agreement with the European Medicines Agency (EMA) and the <National Competent Authority >, would like to inform you of the following:

Summary

- **The cardiovascular risks of Mysimba in patients treated for longer than one year have not been fully determined.**
- **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 when starting treatment with Mysimba.**
- **Physicians should conduct an annual assessment when considering treatment continuation, to ensure no adverse change in cardiovascular risk and maintenance of weight loss.**

Background on the safety concern

Mysimba contains a fixed-dose combination of naltrexone hydrochloride and bupropion hydrochloride. It 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 comorbidities (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.

Uncertainties regarding long-term cardiovascular risks were noted at the time of Mysimba's initial marketing authorisation in 2015. Studies conducted to date have demonstrated the cardiovascular safety and a positive benefit-risk balance for Mysimba treatment lasting up to 12 months. The conduct of a study to further investigate the long-term cardiovascular safety was imposed as a condition of the marketing authorisation. However, long-term study data have not been generated to date.

The remaining concern with the potential long-term cardiovascular risks and the lack of adequate study plan to timely address this uncertainty prompted an EU-wide review of the benefit-risk balance of Mysimba. The review confirmed that the data available so far was insufficient to fully determine the cardiovascular safety beyond 12 months. As a result, further measures have been implemented to minimise the potential risk for cardiovascular events with long-term use of Mysimba. 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 body weigh. This assessment should be conducted in discussion with the patient. The product information and the physician prescriber checklist have been updated accordingly.

In addition, the study design of the INFORMUS cardiovascular outcomes trial currently underway in the United States (NB-CVOT-3, a prospective, pragmatic, randomised, placebo-controlled trial)[1] was reviewed by EMA's human medicines committee (CHMP). With some amendments, the study was considered adequate to further characterise the long-term cardiovascular safety. Results from this study are expected in 2028.

Call for reporting

Healthcare professionals are asked to report any suspected adverse drug reactions in associated with the use of Mysimba in accordance with the national spontaneous reporting system *<include the details (e.g. name, postal address, fax number, web address) on how to access the national spontaneous reporting system>.*

Mysimba is subject to additional monitoring, meaning that it is monitored even more intensively than other medicines.

[1] NCT06098079; Available at: https://clinicaltrials.gov/study/NCT06098079