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Agence nationale de sécurité du médicament et des produits de santé

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DIRECTION DES MÉDICAMENTS EN CARDIOLOGIE, ENDOCRINOLOGIE, GYNECOLOGIE, UROLOGIE
Pôle produit cardiovasculaire, thrombose, métabolisme

Saint-Denis le

Mrs. Sabine Jülicher
Head of Unit, European Commission
Directorate General for Health and Food Safety
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MYSIMBA (naltrexone / bupropion)
EMEA/1/14/988 – EMEA/H/C/003687

Dear Mrs. Jülicher,

Following the draft European Commission decision on marketing authorisation for the medicinal product for human use named Mysimba (naltrexone / bupropion) based on the Committee for Medicinal Products for Human Use (CHMP) positive opinion dated on 19 December 2014, please find France's divergent opinion.

We consider that the overall benefit-risk balance for Mysimba in the claimed indication:

> "*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/m² (obese), or*
> - *≥ 27 kg/m² to < 30 kg/m² (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 (see Section 5.1).*"

is considered negative due to:

1) A limited efficacy in weight management:

The weight loss on Mysimba 32 mg/360 mg was modest as mean weight changes from baseline was less than 10 % in all studies, and the difference to placebo did not exceed 5 % in any study (all-randomised set, Baseline Observation Carried Forward).
Although the main findings in the pivotal studies were that treatment with Mysimba 32 mg/360 mg resulted in statistically significant weight loss compared with placebo in overweight/obese subjects with or without hypertension or dyslipidaemia, as well as in overweight/obese patients with type 2 diabetes mellitus, the weight loss is considered too modest especially considering the safety concerns.
Furthermore, there are uncertainties regarding the maintenance weight loss and/or the rebound effect after treatment discontinuation.
Moreover, the efficacy of Mysimba has only been based on the body weight loss and not on its potential morbidity and mortality benefits during the clinical trial program.

2) Safety concerns:

- Uncertainties regarding neuropsychiatric risks: considering the composition of Mysimba (particularly with bupropion), the risk of depression and suicide is not appropriately described by available data to date of the adoption.

- Uncertainties regarding cardiovascular safety: available data (interim results of the ongoing Cardiovascular Outcome Trial study) to date of the adoption are insufficient and a strong long term data evaluation is mandatory to rule out this risk.

- Poor tolerability which might lead to poor adherence to treatment (about half of the patients discontinued prematurely): the relatively high frequency of such adverse events should affect adherence to treatment.

Overall, for these reasons, we consider that the benefit/risk ratio is negative for Mysimba in the management of obesity.

Therefore, France would like to raise this point to the attention of the Standing Committee and ask for a re-examination of the draft decision during a plenary meeting of the Committee.

Yours sincerely,

Copies :
PJ :

Dominique MARTIN

Directeur général