29 November 2012
EMA/PRAC/747321/2012

PRAC List of questions

To be addressed by the marketing authorisation holder(s) for almitrine-containing medicinal products

Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure number: EMEA/H/A-31/1346

INN/active substance: Almitrine

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The marketing authorisation holders MAH(s) for almitrine containing medicinal products for oral use are requested to provide the following:

Question 1

Please provide information about the indication(s), doses, treatment duration, contraindications, warnings/precautions, and undesirable effects included in the Summary of Product Characteristics (SPC) and the Patient information Leaflet (PIL) of your medicinal product. Please tabulate the main differences between the SPCs/PILs in the different EU Member States.
Please also clarify the clinical use of almitrine containing medical products across the European Union, as single component and via oral route.

Question 2

Please provide information on the current authorisations and marketing status of oral medicines containing almitrine, as single component, in the different Member States, and data on sales figures and estimated patient exposure.

Question 3

Please provide any evidence on efficacy of long-term oral treatment with almitrine, as single component, in patients suffering from chronic respiratory diseases with hypoxemia.
Please provide a critical and documented (published literature and references should be provided) review of the efficacy of oral almitrine (as single component) in the indication relating to chronic respiratory diseases.

Question 4

Please indicate the identified and potential risks associated with oral almitrine.
Please provide a detailed analysis of these risks, including:

- pre-clinical studies;
- clinical trials (include both MAH sponsored and non-sponsored studies);
- postmarketing spontaneous reports (please specify case definitions employed)
- pharmacoepidemiological studies;
- published literature

In reviewing these data, please provide information on the seriousness of the reactions, the frequency and outcome.

Please also provide an analysis of possible risk factors or the predictability of the reactions according to relevant criteria such as age, gender, severity of underlying disease, dose and duration of treatment, indication, co-medications and concomitant/previous illness. Give details of the factors both for and against a causal relationship to almitrine.

Question 5

Please clarify the mechanism for (combined or isolated) peripheral neuropathy and weight loss seen with almitrine. Please also specify according to reporting data, the time range to event onset, outcome (delay, event treatment, sequelae if any), and weight loss amount related to time (maximal, minimal and mean values). In addition, dose dependency and pharmacokinetic relationship of these adverse effects should be thoroughly discussed.

Question 6

Please provide an analysis of the balance of risks and benefits of almitrine, as single component and via oral route, in patients suffering from chronic respiratory diseases with hypoxemia.
Please discuss the place of oral alimitrine among the currently available therapeutic armamentarium for patients with chronic obstructive pulmonary disease (COPD).

Question 7

- Please provide details of any specific measures that have already been taken in order to minimise the risk of peripheral neuropathy and weight loss in patient using oral almitrine and comment on the impact of such measures.

- Please provide proposals and justification with supportive evidence for any risk minimisation measures to address the risks of peripheral neuropathy and weight loss in patient using oral almitrine, including changes to the Summary of Product Characteristics, Labelling and Package Leaflet, which could be taken in order to improve the benefit/risk of almitrine containing medicinal products for oral use. Please also comment on how the impact of such measures should be monitored and assessed.