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Oral almitrine to be withdrawn by EU Member States

PRAC recommendation will be directly implemented following CMDh consensus

The Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), a medicines regulatory body representing the EU Member States, has endorsed the recommendation by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC), that permission to market oral medicines containing almitrine should be withdrawn across the European Union (EU).

As the PRAC recommendation was endorsed by consensus by the CMDh, it will now be implemented directly by the Member States where oral almitrine is authorised, according to an agreed timetable which should be completed by 25 July 2013.

Almitrine is a stimulant of the part of the brain responsible for the breathing reflex. In the EU, it is authorised in France, Poland and Portugal to be taken orally for the treatment of chronic respiratory failure (inability of the lungs to take in oxygen and get rid of carbon dioxide properly), which is associated with hypoxaemia (lower than normal levels of oxygen in the blood). These conditions pose a particular problem in patients with lung conditions known as chronic obstructive pulmonary disease (COPD), where the airways and air sacs inside the lungs become damaged or blocked.

The safety review of oral almitrine was requested by the French medicines agency, the National Agency for the Safety of Medicine and Health Products (ANSM), because of concerns about side effects and a view that the available evidence did not support the use of the medicine in the current management of COPD. The PRAC concluded that there is a clear association between oral almitrine treatment and potentially serious and long-lasting peripheral neuropathy (damage to the nerves in the hands and feet) and significant weight loss that further weakens patients. The PRAC noted that cases continue to be reported even after additional precautions on the use of the medicines were put in place. Furthermore, oral almitrine is no longer included as a recommended therapy in international treatment guidelines for the management of COPD.

The CMDh agreed with the PRAC conclusion that the benefits of these medicines do not outweigh their risks, and adopted a final position that the marketing authorisations should be withdrawn throughout the EU.

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Information to patients

- Almitrine, a medicine that was authorised several years ago to be taken by mouth to help breathing, is not one of the currently recommended treatments for lung diseases.
- Because almitrine has been shown to carry a risk of damage to the nerves in the hands and feet as well as weight loss, and because a number of alternative treatments are now available, it will be withdrawn across the EU.
- If you are taking an almitrine-containing medicine, you should make a non-urgent appointment with your doctor to review your treatment. Patients who have any questions should speak to their doctor or pharmacist.

Information to healthcare professionals

- Oral almitrine-containing products should no longer be prescribed or dispensed to patients.
- Patients being treated with oral almitrine should have their treatment reviewed at the next scheduled appointment, and appropriate alternative treatments should be considered.
- Pharmacists should refer patients presenting a new or repeat prescription to their treating physician.
- Prescribers and pharmacists will be sent a letter giving them further information on the withdrawal of oral almitrine.

The Agency's recommendations are based on an EU-wide safety review.

- The safety review confirmed a clear association of oral almitrine therapy with significant weight loss and peripheral neuropathy (which can be long-lasting and possibly irreversible). The company marketing almitrine identified 795 spontaneously reported cases of weight loss and 2,304 cases of peripheral neuropathy over the 30-year period that the medicine has been marketed (representing several million patient months of treatment). In 489 cases, neuropathy was indicated to have been irreversible, or to have led to sequelae. Additional results from clinical studies suggested that neuropathy was most common after three months or more of treatment.
- The PRAC noted that cases of weight loss and peripheral neuropathy have continued to be reported, despite the introduction of a number of risk minimisation measures, including sequential administration (two months treatment followed by a one-month break), dose reduction and appropriate warnings in the product information. Of the spontaneous reports, 7 cases of weight loss and 20 of peripheral neuropathy had been reported since September 2003 when all these measures were in operation. In three of the latter cases, patients were rechallenged with almitrine and this led to a recurrence of neuropathic symptoms, including sequelae in two.
- The understanding of COPD and the therapeutic options for its management have changed considerably since the original authorisation of oral almitrine. Almitrine is not one of the treatments currently recommended in international guidelines for COPD management (GOLD), and the available evidence does not support a clinical benefit for long-term oral treatment with the medicine.

In view of the potentially serious adverse effects and the lack of an established role in the current management of hypoxaemic pulmonary disease, the benefit-risk of oral almitrine is no longer considered favourable.

More about the medicine

Almitrine is a respiratory stimulant, a medicine that stimulates the part of the brain responsible for the breathing reflex. In the EU, it is authorised in France, Poland and Portugal as 50-mg tablets (Vectarion, Armanor) for the treatment of chronic respiratory failure (inability of the lungs to take in oxygen and get rid of carbon dioxide properly), which is associated with hypoxaemia (lower than normal levels of oxygen in the blood).

More about the procedure

The review of oral almitrine-containing medicines was initiated in December 2012 at the request of France, under Article 31 of Directive 2001/83/EC.

A review of these data was first conducted by the Pharmacovigilance Risk Assessment Committee (PRAC). As almitrine-containing medicines are all authorised nationally, the PRAC recommendations were sent to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which adopted a final position. The CMDh, a body representing EU Member States, is responsible for ensuring harmonised safety standards for medicines authorised via national procedures across the EU.

As the CMDh position was adopted by consensus, it will be directly implemented by the Member States where oral almitrine-containing medicines are authorised. In line with the PRAC recommendation, the marketing authorisations for oral almitrine-containing medicines will be revoked in the affected Member States, which means that permission for the medicines to be marketed has been withdrawn.