

## **Annex II**

### **Scientific conclusions and grounds for the revocation of the marketing authorisations**

## **Scientific conclusions and grounds for the revocation of the marketing authorisations**

The CMDh, having considered the PRAC recommendation dated 16 May 2013 with regards to the Almitrine containing medicinal products for oral use, agrees with the recommendation therein as stated below:

### **Overall summary of the scientific evaluation of Almitrine containing medicinal products for oral use by PRAC**

Almitrine bismesylate is indicated in patients with respiratory failure with hypoxemia related to obstructive bronchitis.

The first Marketing Authorisation in the EU was granted in France on 10 December 1982. Almitrine containing medicinal products for oral use are currently authorised in 3 European Member States (France, Poland and Portugal) and only marketed in France and Poland (see Annex I for the list of almitrine containing medicinal products for oral use authorised in the EU).

On 27 November 2012 France informed the European Medicines Agency, pursuant to Article 31 of Directive 2001/83/EC, of their consideration to review the benefit risk balance of almitrine for oral use in the treatment of chronic respiratory diseases resulting from the evaluation of data relating to pharmacovigilance.

In France, almitrine containing medicinal products for oral use have been under close monitoring due to serious adverse reaction . The reported reactions consisted mainly of peripheral neuropathy and weight loss. France has taken a number of national regulatory actions to minimise the risk of these adverse reactions associated with almitrine for oral use. In November 2012 the French National Competent Authority considered that the above-mentioned major safety concerns were not fully controlled in clinical practice despite the risk minimisation measures in place. This was supported by the fact that cases of peripheral neuropathy continued to be reported from September 2003 to November 2012 despite the implemented minimisation measures (recommendation for a sequential scheme of administration and dose adjustment initially, followed by contra-indications and warnings). In addition, France had concerns with regards to the benefit of almitrine in its approved indications.

### **Safety**

Based on the data from clinical studies and post-marketing experience, the two main safety concerns with almitrine are peripheral neuropathy and weight loss. Risk minimisation measures (reduction of the dose and implementation of a sequential treatment scheme ) were implemented since the initial marketing authorisation.

Long-term use of almitrine bismesylate is currently recommended at a dose level of 50 to 100 mg per day with limitation of the dose at 50 mg per day in patients with body weight less than 50 kg. After 3-month treatment, maintenance therapy of the sequential type is recommended: a 1-month interval for every 2 months treatment.

#### *Data from clinical trials*

Almitrine for oral use was studied in several clinical studies. Among the clinical studies in Chronic Obstructive Pulmonary Disease (COPD) patients, only those with more than 30 patients treated with therapeutic doses of almitrine for at least 3-month were selected for an efficacy and safety

overview. A total of 11 published clinical studies which became available after the initial Marketing Authorisation were reviewed. Taken together, these clinical trials enrolled 2036 patients (1380 under almitrine, 656 under placebo). The first trials, conducted with non-sequential treatment, account for 1670 patients (1006 following a double blind, placebo controlled design). The last trials, conducted with sequential treatment and following a double blind placebo controlled design, account for 366 patients. The treatment duration was up to 2 years.

In published clinical studies with continuous administration<sup>1234567</sup>, peripheral neuropathies and weight loss were encountered when the study duration was longer than 3 months, indicating that the duration of continuous exposure have played a role in their development.

The doses of 100-200 mg of almitrine continuously were associated with a higher incidence of adverse effects and withdrawals compared to placebo.

In addition to peripheral neuropathies with abnormal sensations in the lower limb or paraesthesia and weight loss up to -6%, in the publications reporting clinical studies with continuous administration, the following adverse events were also more frequent in the almitrine groups:

- Respiratory events, mainly due to awareness of respiratory movements
- Digestive events (nausea, burning sensation and sensation of epigastric heaviness, dyspepsia),
- Central nervous events (sleep disorders such as insomnia, drowsiness, agitation, anxiety, palpitations, dizziness)

Based on the available publications of clinical studies with sequential treatment scheme<sup>891011</sup> (i.e. two months of treatment followed by one month treatment interruption), the rate of withdrawal remained predominant in the almitrine groups as compared to placebo groups in the majority of the publications.

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<sup>1</sup> Ansquer J.C., Bertrand A., Blaive B., Charpin J., Chretien J., Decroix G., Kalb J.C., Lissac J., Michel F.B., Morere P., Paramelle B., Pariente R., Perrin-Fayolle M., Rochemaure J., Sadoul P., Voisin C. The therapeutic value and acceptability of Vectarion 50 mg coated tablets (Almitrine bismesylate) at the dose of 100 mg per day. *Rev Mal Resp* 1985 ; 2: S61-67 (PE10644)

<sup>2</sup> Arnaud F., Bertrand A., Charpin J., Chretien J., Decroix G., Guerrin F., Kalb J.C., Lissac J., Michel F.B., Morere P., Paramelle B., Pariente R., Perrin-Fayolle M., Rochemaure J., Voisin C.. Long-term Almitrine bismesylate treatment in patients with chronic bronchitis and emphysema: a multicentre double-blind placebo controlled study. *Eur J Respir Dis* 1983; 64(Suppl 126):323-330 (PE10377)

<sup>3</sup> Bakran I., Vrhovac B., Stangl B., Tabori D., Ivicovic A., Todic V., Kandare F. Double- blind placebo controlled clinical trial of Almitrine bismesylate in patients with chronic respiratory insufficiency. *Eur J Clin Pharmacol* 1990; 38(3) : 249-253 (PE11220)

<sup>4</sup> Bardsley P.A., Howard P., De-Backer W., Vermeire P., Mairesse M., Ledent C., Radermecker M., Bury T., Ansquer J.. Two years treatment with Almitrine bismesylate in patients with hypoxic chronic obstructive airways disease. *Eur Respir J* 1991; 4: 308-310 (PE11144)

<sup>5</sup> Gonzales-Ruiz J.M., Villamor-Leon J., Garcia-Satue J.L., Sanchez-Agudo L., Calatrava J.M., Carreras J.. Treatment of chronic respiratory failure by Almitrine bismesylate. *Rev Clin Esp* 1994; 194:1007-12 (PE20805).

<sup>6</sup> Marsac J. The assessment of Almitrine bismesylate in the long-term treatment of chronic obstructive bronchitis. *Eur J Respir Dis* 1986; 69(Suppl 146):685-693 (PE10387)

<sup>7</sup> Voisin C., Howard P., Ansquer J.C. Almitrine bismesylate: a long-term placebo- controlled double-blind study in COAD. Vectarion International Multicentre Study Group. *Bull Eur Physiopathol Respir* 1987 ; 23(suppl 11) : 169-182 (PE10837)

<sup>8</sup> Bardsley P.A., Howard P., Tang O., Empey D., Harisson B., Peake M.D., O'Reilly J., Riordan J.F., Wilkinson J., Arnaud F., Jarratt J.A. Sequential treatment with low dose Almitrine bismesylate in hypoxaemic chronic obstructive airways disease. *Eur Respir J* 1992; 5(9): 1054-1061 (PE11128)

<sup>9</sup> Gorecka D., Sliwinski P., Palasiewicz G., Pachocki R., Zielinski J.. Effects of Almitrine bismesylate on arterial blood gases in patients with chronic obstructive pulmonary disease and moderate Hypoxaemia: A Multicentre, Randomised, Double-Blind, Placebo- Controlled Study. *Resp.* 2003 ; 70 : 275-283 (PE32001)

<sup>10</sup> Nowak D., Wywiol A., Magnussen H.. Almitrine in the treatment of chronic obstructive pulmonary disease with hypoxemia - a multicentre clinical study comparing two dosages. *Pneumology* 1998 Mar;52(3):121-7 (PE24412)

<sup>11</sup> Weitzenblum E., Arnaud F., Bignon J., Boutin C., Brune J., Castaing Y., Courty G., Derenne J.P., Duroux P., Freour P., Muir J.F., Paramelle B., Philip-Joet F., Poirier R., Pouget J., Senant J., Tonnel A.. Sequential administration of a reduced dose of Almitrine in patients with chronic obstructive lung disease. Multicentre controlled trial. *Rev Mal Resp* 1992; 9: 455-463 (PE11153)

### Spontaneous reports

In addition to publications of clinical studies, the PRAC reviewed post marketing data provided by the MAH.

With regards to peripheral neuropathy, a total of 2304 cases of peripheral neuropathy have been spontaneously reported in patients exposed to almitrine since the launch of the product (from 1983 to December 2012). Spontaneous reports of peripheral neuropathies persist even after the introduction of sequential administration scheme. During the period September 2003 to December 2012, 20 cases of peripheral neuropathies were reported, suggesting that the risk minimisation measures are not able to prevent the occurrence of these reactions. The decrease in reporting of peripheral neuropathy mentioned by the MAH, is probably mainly related to the decrease in sales over the last 10 years.

Globally, an important proportion of cases had an outcome reported as not recovered or recovered with sequelae (489 cases out of the 2304 reported, i.e. 21.2%). The PRAC noted that most cases of peripheral neuropathies reported from September 2003 to December 2012 were not recovered or recovered with sequelae. Even if occurrence of peripheral neuropathy in COPD patients with associated conditions could be considered as a confounding factor, the occurrence of cases with positive rechallenge with almitrine during the post-marketing experience is strongly in favour of a causal relationship between almitrine and peripheral neuropathies.

Regarding weight loss, 795 cases were reported since launch, some of them severe. The mean time to onset for the cases reported was 5 months but time to onset was variable ranging from 15 days to 2,5 years. In 50% of the cases, a neuropathy was also reported. The PRAC noted that weight loss reported led to almitrine discontinuation in 90,9% of the cases.

An important proportion of cases seems to have been reported with an outcome as not recovered during the period from September 2003 to December 2012 (5 cases of the 7 reported).

Weight loss observed in patients with respiratory insufficiency is progressive. However, the PRAC noted that weight loss reported with almitrine could occur faster and be more severe than what is commonly observed in chronic respiratory insufficiency. Hypoxemia alone is not sufficient to explain severe weight loss reported with almitrine. This adverse effect was also clearly recognised in the trials comparing almitrine at high doses to placebo.

Based on the above the PRAC considered that the use of oral almitrine is associated with serious adverse peripheral neuropathy and weight loss reactions sometimes with sequelae.

In addition, the PRAC noted that the mechanism of these 2 adverse reactions remains unknown. The MAH has never performed trials or investigations to document/establish the mechanism of action of these adverse effects. No published data focusing on the proper mechanism of almitrine in the occurrence of those adverse events was provided by the MAH.

Concerns have also been raised with regards to the potential risks of hepatobiliary disorders, skin disorders and cytopenia with the use of oral almitrine.

Overall, based on the available published data and data from spontaneous reports, the PRAC considers that almitrine use is associated with serious cases of peripheral neuropathy, some with positive rechallenge, and weight loss. Important weight losses and peripheral neuropathies which can potentially not recover or lead to sequelae, are still reported with almitrine despite risk minimisation measures in place for several years. Further risk minimisation measures, as proposed by the MAH, such as additional amendments to the product information (restriction of the

indication and contra-indications), communication material (dear Health Care Professional Communication) and restricted prescription (restriction to one month for pneumologists and hospital's use) were also considered during the discussions. Based on the published literature and post marketing data, the PRAC is of the view that the risk minimisation measures proposed by the MAH would not be able to adequately reduce the risks of serious adverse reactions to a clinically acceptable level: any additional communication on risks of neuropathies and weight loss, already well known to prescribers, would not contribute to a safer use of the product. Moreover, no data is available to support any benefit of almitrine in the restrictive indication proposed by the MAH (patient with PaO<sub>2</sub>: 55 mmHg < PaO<sub>2</sub> < 65 mmHg).

Overall, a significant number of cases with outcomes reported as not recovered or recovered with sequelae is not acceptable to the PRAC.

### **Efficacy**

In view of the 11 above mentioned published clinical studies, it is acknowledged that efficacy results among clinical studies are contradictory and extrapolations not feasible. PRAC noted that in the clinical trials with results in favour of almitrine, effect of almitrine could have been overestimated as a high rate of patients withdrew predominantly in the almitrine group as compared to placebo (Voisin and al, 1987 and in most of all the clinical trials).

The PRAC considered that many of the publications reported that a clinical benefit of oral almitrine could not be seen in terms of exacerbations or hospitalisation, exercise capacity, clinical outcome, survival, or quality of life. No effect was nor observed on pulmonary functional status.

One of the proposed further risk minimisation measures by the MAH was a restricted indication in patients with PaO<sub>2</sub> between 55 mmHg and 65 mmHg or as adjuvant treatment to Long Term Oxygen Therapy (LTOT).

However, no data supports the restrictive indication proposed by the MAH. In addition, the benefit claimed by the MAH that long-term oxygen therapy can be delayed with almitrine is not substantiated by supporting data. Consideration that long-term oxygen therapy can be discontinued, delayed or even avoided with almitrine is not based on scientific or clinical evidence. No benefit has been demonstrated when almitrine was used as an adjuvant of that intervention. The PRAC is of the opinion that almitrine cannot be considered as an alternative to LTOT for which reduction in mortality has been achieved.

The uncertainties relating to the mechanisms of action implying the vasoconstriction of pulmonary vasculature (which is inverse to the beneficial effect of LTOT on pulmonary arterial pressure) was noted by the PRAC.

Finally the PRAC noted that the current international consensus for the management of COPD and chronic hypoxemia (Global Initiative for Obstructive Lung Disease (GOLD) and other practical recommendation) does no longer refer to the use of almitrine.

Based on the above, the PRAC considered that the available efficacy data, including data which became available since the initial marketing authorisation, showed only very limited efficacy of oral almitrine in its approved indications which does not translate in evidence of a benefit for patients in the current context of the therapeutic strategy and knowledge acquired in respiratory diseases.

### **Overall conclusion**

The PRAC considered that the use of oral almitrine is associated with serious adverse peripheral neuropathy and weight loss reactions sometimes with sequelae.

The PRAC considered the risk minimisations measures already implemented (reduction of the dose and implementation of a sequential treatment scheme) to mitigate the risk of neuropathies and weight loss. Despite sequential doses regimen and amendments in the SmPC, the PRAC noted serious cases of neuropathy and weight loss continued to be reported, including some cases with positive rechallenge, and leading sometimes to sequelae.

Further risk minimisation measures such as additional amendments to the product information (restriction of the indication and contra-indications), communication material (dear Health Care Professional Communication) and restricted prescription were also considered during the discussions. The PRAC is of the view that the risk minimisation measures proposed by the MAH would not be able to adequately reduce the risks of serious adverse reactions to a clinically acceptable level: any additional communication on risks of neuropathies and weight loss, already well known to prescribers, would not contribute to a safer use of the product. Moreover, no data is available to support any benefit of almitrine in the restrictive indication proposed by the MAH (patient with PaO<sub>2</sub>: 55 mmHg < PaO<sub>2</sub> < 65 mmHg).

Further to the review of the available efficacy data, including data which became available since the initial marketing authorisation, the PRAC concluded that the available data only showed very limited efficacy of oral almitrine in its approved indications which does not translate in evidence of a benefit for patients in the current context of the therapeutic strategy and knowledge acquired in respiratory diseases. Besides, the PRAC also noted that the knowledge in physiopathological mechanism and management of COPD (including life expectancy in COPD) has been considerably improved. Finally the PRAC noted that the current international consensus for the management of COPD and chronic hypoxemia (Global Initiative for Obstructive Lung Disease (GOLD) and other practical recommendation) does no longer refer to the use of almitrine.

During the assessment, the MAH confirmed that all the available data have been provided and that they will not be able to provide any further data to demonstrate the clinical benefit of oral almitrine in the management of chronic hypoxemia in COPD. The PRAC took in account the MAH's position.

The PRAC therefore concluded that the benefit-risk balance of almitrine containing medicinal products for oral administration is not favourable.

In the view of the negative benefit risk balance, patients will need to be switched to alternative therapies. The NCAs should undertake timely actions allowing an appropriate switching of patients to other therapeutic alternatives.

## Grounds for PRAC recommendation

Whereas,

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, for almitrine containing products for oral administration (see Annex I).
- The PRAC considered the totality of the data available for almitrine containing products for oral administration in relation to the risk of peripheral neuropathy and weight loss. This included data from the Member States and published literature data which became available since the original marketing authorisations and the MAH's response.
- The PRAC considered that the use of oral almitrine is associated with serious adverse peripheral neuropathy and weight loss reactions sometimes with sequelae.
- The PRAC considered, based on the assessment of the impact of risk minimisation measures already implemented (reduction of the dose and implementation of a sequential treatment scheme) and on the published literature, that the additional risk minimisation measures proposed by the Marketing Authorisation Holder and discussed during the assessment would not be able to adequately reduce the risks of serious adverse reactions to a clinically acceptable level.
- The PRAC considered that the available efficacy data, including data which became available since the initial marketing authorisation, showed only very limited clinical efficacy of almitrine in its approved indications.
- The PRAC took into account the MAH's position that all the available data have been provided and that there was no possibility to provide additional data for the demonstration of the clinical benefit of oral almitrine in chronic obstructive pulmonary disease (COPD).
- The PRAC therefore concluded, in view of the available data, that the risks of serious peripheral neuropathy and weight loss adverse reactions associated with the use of almitrine-containing medicinal products for oral administration in the treatment of respiratory failure with hypoxemia related to obstructive bronchitis outweigh the limited benefits.

The PRAC, as a consequence, concluded that pursuant to Article 116 of Directive 2001/83/EC the risk-benefit balance for almitrine containing products for oral administration is not favourable.

Therefore, in accordance with Articles 31 and 32 of Directive 2001/83/EC, the PRAC recommends the revocation of the marketing authorisations of the marketing authorisations for all medicinal products referred to in Annex I.

## CMDh agreement

The CMDh, having considered the PRAC recommendation dated 16 May 2013 pursuant to Article 107k(1) and (2) of Directive 2001/83/EC, reached an agreement on the revocation of the marketing authorisations of almitrine containing products for oral use.

The timetable for the implementation of the agreement is set out in Annex III.