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SCIENCE MEDICINES HEALTH

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## Assessment report for almitrine-containing medicinal products for oral use

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

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

Assessment Report as adopted by the PRAC with all information of a confidential nature deleted.



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## 1. Background information on the procedure

On 27 November 2012, further to evaluation of data resulting from pharmacovigilance activities, France informed the European Medicines Agency, pursuant to Article 31 of Directive 2001/83/EC, of their consideration that the risk benefit balance of almitrine for oral use has become unfavourable and therefore it was in the interest of the Union to refer the matter to the PRAC.

## 2. Scientific discussion

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 reactions . 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), and despite a strong decrease in sales. In addition, France had concerns with regards to the efficacy of almitrine in its approved indications.

### 2.1. Clinical aspects

In its assessment the PRAC considered the data submitted by the MAH as well as published literature and data available to the Member States.

#### 2.1.1. 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. To address these reactions, 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.

## **Spontaneous reports**

The number of cases for peripheral neuropathy and weight loss events was closely monitored through an official national Pharmacovigilance survey by the French Competent Authority. During the post-marketing 30-year period (10 December 1982 – 31 December 2012), the following cases were reported:

- 2304 cases of peripheral neuropathy, amounting for 3535 events. The majority of cases (93.7%) were reported as non-serious.
- 795 cases of weight loss, amounting for 795 events. The majority of cases (90.8%) were reported as non-serious.

In view of these ADRs and published clinical studies, risk minimization measures were implemented during the life-cycle of the oral almitrine through changes of the Summary of Product Characteristics, among which:

- Introduction of a sequential administration scheme in the section 4.2 Posology and Method of administration, i.e. two months of treatment followed by one month treatment interruption, since May 1986.
- A dose adjustment on body weight in the section 4.2 Posology and Method of administration, i.e. limitation of the dose at 50mg/day in patients with body weight < 50kg since May 1986, contra-indications and necessity to stop the treatment in case of weight loss and/or signs of neuropathy in sections 4.3 Contraindications and 4.4 Special warnings and precautions for use, since May 1986 and September 2003.

### **1. Peripheral neuropathy**

Peripheral neuropathies were reported in the first years of post-marketing experience. The French Competent Authorities closely monitored the number of cases for these events.

The MAH performed a global and a focused analysis (aiming at reviewing specifically the reporting period from September 2003 to December 2012 i.e. further to establishment of minimisation measures in 1986 and subsequently in 2003) for cases of peripheral neuropathy.

#### **Global analysis**

During the 30-year cumulative period, a total of 2304 cases of peripheral neuropathies, amounting for 3535 events, were identified from the MAH's pharmacovigilance database. A majority of cases (2161, 93.7%) were reported as non-serious. The other (144 cases, 3.6%) were reported as serious.

When documented, the time to onset of adverse reaction ranges from 10 days to 3.5 years after initiation of treatment. The most frequent values for the time to onset are in the order of months (mean onset 11 months).

Among the 2304 cases, cases are also associated to a weight decrease reported as adverse event.

The action taken towards the drug was withdrawal in 2118 cases (91.9%), dose reduction in 39 cases (16.9%), dose unchanged in 66 cases (2.8%) or unknown in 82 cases (3.5%).

The distribution of the cases' outcome is as follows:

- Fatal: 3 cases (0.1%)

- Not recovered and/or Recovered with sequelae: 489 cases (21.2%)
- Recovering and Recovered: 1317 cases (57.1%)
- Unknown: 495 cases (21.4%)

In the 3 fatal cases (2 of them with concomitant weight loss), the reported cause of death was worsening of respiratory failure (natural course of the disease), not ascribed to the drug by the reporter.

#### Analysis of cases for period September 2003-December 2012

A focused analysis was performed, covering the period from September 2003 to December 2012 ( i.e. further to establishment of minimisation measures, recommendation for a sequential scheme of administration aiming to decrease occurrence of neuropathy and weight loss as well as dose adjustment since 1986, and contra-indications and warnings since 2003).

During the period September 2003 to December 2012, a total of 20 cases of peripheral neuropathies were reported from various sources, which represents an average of 2.5 cases per year. The indication is COPD in 9 cases, is pulmonary alveolar hypoventilation in 1 case, interstitial lung disease in another case and not specified in the 9 remaining cases. For the patients who were prescribed the drug in the correct indication, age, gender and concomitant conditions as well as their treatments are consistent with the average COPD population.

Documentation of the neuropathies, according to the case narratives, can be considered adequate in only half of the cases.

3 probable cases correspond to situations with positive rechallenge.

- One case (recovered with sequelae) with reintroduction of the drug after a 18-month therapeutic window during which the symptoms had abated
- One case (recovered), with sequential treatment scheme, the symptoms regressing during the windows, and reappearing – more and more intense – at reintroduction within a regular sequential treatment
- One case (recovered with sequelae), with reappearance upon one episode of drug reintroduction of the pain that had previously regressed after withdrawal of the drug.

Apart from chronic hypoxemia, alternative explanations for the peripheral neuropathies can be diabetes mellitus (3 cases), alcohol abuse (3 cases), hypothyroidism (1 case).

#### Conclusion on peripheral neuropathy

From the global part of the analysis provided by the MAH, the PRAC concluded that the characteristics of patients (hypoxemic COPD) reported in the cases are consistent, in terms of gender, age, etc. with those of the targeted disease, as well as are their medical history and their concomitant treatments. The PRAC noted though that the majority of the cases date back from the period 1985-1988, and are not always optimally documented. However, the PRAC is of the view that no definite pattern predictive for the development of peripheral neuropathy emerges from the patient characteristics and/or case narratives. In addition, the mean time to onset for the 2304 cases reported was 11 months but seems very variable (ranged from 10 days to 3,5 years).

The PRAC noticed that 20 cases of peripheral neuropathies have been reported from September 2003 to December 2012 despite minimisation measures (recommendation for a sequential scheme of

administration and dose adjustment since 1986, and contra-indications and warnings since 2003), and despite a dramatic decrease of sales data. Of them at least 4 cases (with one positive rechallenge) have been reported in patients even when the sequential administration schema was well followed, showing that it did not prevent occurrence of peripheral neuropathies.

The PRAC also noted that of the 20 cases reported after September 2003, a positive rechallenge has been reported in 3 cases which strongly suggest the role of almitrine in the occurrence of those effects. The outcome "recovering with sequelae" was reported in 2 of the 3 positive rechallenge. Globally, the PRAC concluded on an important proportion of cases with an outcome reported as "not recovered" or "recovered with sequelae" (489 cases of the 2304 reported, i.e. 21.2%).

## **2. Weight loss**

During the 30-year cumulative period, a total of 795 cases of weight loss, amounting for 795 events, were identified from the MAH's pharmacovigilance database.

The implementation of the first minimization measures (new therapeutic scheme, i.e. two months of treatment followed by one month treatment interruption) in May 1986, was followed by a rapid and steady decline in the number of reported cases of weight decrease.

### Global analysis

A majority of cases (722, 90.8%) were reported as non-serious. The other (73 cases, 9.1%) were reported as serious.

Apart from COPD and respiratory failure, most of the patients often have a history of diseases frequently associated to COPD, such as hypertension (118 cases), coronary artery disease (60 cases), cardiac failure (40 cases), diabetes (38 cases), alcohol abuse (188 cases), depression (39 cases) and obesity (41 cases).

When documented, the value ranges from 15 days to 2.5 years after initiation of treatment. The most frequent values for the time to onset are in the order of months (mean onset 5 months).

Among the 795 cases, cases are associated to a neuropathy reported as adverse event.

The action taken towards the drug was withdrawal in 723 cases (90.9%), dose reduction in 22 cases (2.7%), dose not changed in 26 cases (3.2%) and action being unknown in 24 cases (3.0%).

### Analysis of cases for period September 2003-December 2012

A majority of cases (722, 90.8%) were reported as non-serious. The other (73 cases, 9.1%) were reported as serious.

### Conclusion on weight loss

A total of 795 cases of weight loss have been spontaneously reported in patients exposed to almitrine since the launch of the product. The mean time to onset for cases reported was 5 months but times to onset ranged from 15 days to 2.5 years. In some cases, a neuropathy was also reported. It should be noted that the weight loss reported led to almitrine discontinuation in 90.9% of the cases. It should be noted that the weight loss reported led to almitrine discontinuation in 90.9% of the cases.

In some cases important weight loss occurred rapidly after almitrine initiation.

Of them, 7 cases have been reported from September 2003 to December 2012 despite minimisation measures (recommendation for a sequential scheme of administration aiming to decrease occurrence of neuropathy and weight loss since 1986, dose adjustment since 1986, and contra-indications and warnings since 2003), and despite a dramatically decrease of sales data. Of them at least one case has been reported in patients even when the sequential administration schema was well followed, showing that it did not prevent the occurrence of weight loss.

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

### **Data from clinical trials**

Several clinical studies with almitrine were performed, before and after implementation of the sequential therapeutic scheme. Efficacy and safety findings though publications are presented below.

Almitrine for oral use was studied in several clinical studies (cf. 2.1.2 Efficacy). 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.

The percentage of premature withdrawals is globally high in all the studies and groups (almitrine or placebo, from 16 to 67% and from 5.9 to 48%, respectively).

The number of patients who reported adverse events for the different treatment groups in placebo-controlled studies with continuous administration is given in table 1 below.

**Table 1.** Adverse events for the different treatment groups in placebo-controlled studies with continuous administration of almitrine.

Study	ARNAUD and al. 1983				VOISIN and al. 1987				BAKRAN and al., 1990				BARDSLEY and al. 1991 (1)*			
	200-100 mg 6 months		Placebo 6 months		100-200 mg 12 months		Placebo 12 months		100mg 3 months		Placebo 3 months		100-200 mg 24 months		Placebo 12 months	
Number of patients	100		100		344		357		19		16		43		46	
AE: Total number (%)	<b>34</b> (34%)		<b>39</b> (39%)		<b>245</b> (71%)		<b>138</b> (39%)		<b>6</b> (32%)		<b>3</b> (19%)		<b>14</b> (33%)		<b>5</b> (11%)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Respiratory	12	12.0	7	7.0	59	17.2	37	10.4	2	10.5	2	12.5	4	9.3	1	2.2
Digestive	11	11.0	15	15.0	75	21.8	57	16.0	2	10.5	-	-	4	9.3	2	4.3
CNS	6	6.0	12	12.0	61	17.7	36	10.1	-	-	-	-	-	-	-	-
PNS	-	-	-	-	50	14.5	8	2.2	-	-	-	-	6	14.0	2	4.3
Cardiovascular	4	4.0	3	3.0	-	-	-	-	-	-	-	-	-	-	-	-
Skin	1	1.0	2	2.0	-	-	-	-	1	5.3	-	-	-	-	-	-
Miscellaneous	-	-	-	-	-	-	-	-	1	5.3	1	6.3	-	-	-	-

\* The first 12 months are part of the Voisin study

CNS= central nervous system, PNS peripheral nervous system, NA= not available,

AE= adverse event, ADR= adverse drug reaction, WAE= adverse event leading to treatment withdrawal

In the studies with continuous administration, the following adverse events were 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 event (sleep disorders such as insomnia, drowsiness, agitation, anxiety, palpitations, dizziness,
- Peripheral neuropathies with abnormal sensations in the lower limb or paraesthesia.
- Weight loss up to –6% (Voisin, 1987) were observed in the almitrine group

In the studies with sequential administration, respiratory events were not more frequent in the almitrine groups, the incidence of digestive events and nervous system events were less than with continuous doses but remained slightly more frequent with almitrine. Weight losses from –2 to –5% were observed.

**Table 2.** Adverse events for the different treatment groups in placebo-controlled studies with sequential administration of almitrine.

Study	WEITZENBLUM and al, 1992				BARDSELY and al, 1992 (2)				GORECKA and al, 2003			
	100 mg sequential 12 months		Placebo 12 months		50-100 mg sequential 6 months		Placebo 6 months		100mg sequential 12 months		Placebo 12 months	
Treatment daily dose duration												
Number of patients	65		37		50		35		57		58	
AE: Total number (%)	32 AE 24 patients (36.9%)		13 AE 11 patients (29.7%)		13 WAE (26%)		6 WAE (17%)		40 patients (70%)		42 patients (72%)	
	n	%	n	%	n	%	n	%	n	%	n	%
Respiratory	3	4.6	0	-	na	na	na	na	29	50.8	36	62.1
Digestive	10	15.4	1	2.7	na	na	na	na	10	17.5	8	13.8
PNS or CNS	11	16.9	7	18.9	na	na	na	na	12	21.1	10	17.2
Cardiovascular	4	6.2	1	2.7	na	na	na	na	13	22.8	21	36.2
Skin	1	1.5	2	5.4	na	na	na	na	-	-	-	-
Psychiatric	1	1.5	1	2.7	na	na	na	na	7	12.3	10	17.2
Weight loss	-	-	-	-	na	na	na	na	4	7.0	0	0
Others	2	3.1	1	2.7	na	na	na	na	na	na	na	na

CNS= central nervous system, PNS peripheral nervous system, NA= not available,  
AE= adverse event, ADR= adverse drug reaction, WAE= adverse event leading to treatment withdrawal



**Table 3.** Weight decrease and peripheral nervous system (PNS) events observed in placebo-controlled studies with almitrine.

Study	Treatment Dosage per day	Duration	N	Weight change		PNS events	
				kg	%	n	%
ARNAUD et al, 1983	200mg for 3 months then 100mg for 3 months	6 months	200/ 1	-	-	-	-
VOISIN et al, 1987	100-200 mg	12 months	344	-4.2kg	-6%	50	14.5%
	Placebo	12 months	357	+0.4kg	+0.5%	8	2.2%
BAKRAN et al., 1990	100 mg	3 months	23	NA	NA	-	-
	Placebo	3 months	17	NA	NA	-	-
BARDSLEY et al, 1991 (1)*	100-200 mg	24 months	43	NA	NA	6	13.9%
	Placebo	24 months	46	NA	NA	2	4.3%
WEITZENBLUM and al, 1992	100 mg sequential	12 months	65	-1.4kg	-2%	6	9.2 %
	Placebo	12 months	37	+1.2kg	+1.8%	3	8.1 %
BARDSLEY and al, 1992 (2)	50 to 100 mg sequential	6 months	50	-3.6kg	4.9%	2	4.0%
	Placebo	6 months	35	0.6kg	0.9%	2	5.7%
GORECKA and al, 2003	100 mg sequential	12 months	57	NA	NA	7	12.3%
	Placebo	12 months	58	NA	NA	4	6.9%

\* The first 12 months are part of the Voisin study

NA: not available

Voisin et al, 1987: Peripheral neuropathy (essentially paraesthesia and less commonly pain in the lower limbs) were observed in the almitrine group after an average of 7 months follow-up and led to the withdrawal of 4% of the included patients.

#### Conclusion on clinical data

Among the clinical published studies provided by the MAH, the sequential scheme of administration appeared to provide higher tolerance but the PRAC noticed that the rate of withdrawals remained predominant in the Almitrine groups as compared to placebo groups with the major proportion of withdrawal related to adverse effects with Almitrine.

#### Discussion on potential mechanism of action of Almitrine on peripheral neuropathies and weight loss

A higher rate of peripheral neuropathies and weight loss clearly appeared with almitrine when compared to placebo in clinical trials and the role of almitrine to induce those adverse effects has been undoubtedly recognised by all practitioners and the MAH itself since the beginning of the use of almitrine. However, the MAH has never performed trials or investigations to document/establish the mechanism of action of those identified adverse effects. The response of the MAH doesn't provide any published data focusing on the proper mechanism of almitrine in the occurrence of those adverse events.

The PRAC is of the opinion that the mechanism of these 2 risks remains unknown.

### **Conclusion on 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, 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 (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.

### **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 contraindications), 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  $\text{PaO}_2: 55 \text{ mmHg} < \text{PaO}_2 < 65 \text{ mmHg}$ ).

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

## 2.1.2. Efficacy

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

The PRAC considered the dataset submitted by the MAH (which was exclusively based on published references) as well as additional information provided by Members States during the assessment (such as the Sans Torres, 2003 publication).

Among the publications in Chronic Obstructive Pulmonary Disease (COPD), only those reporting clinical studies conducted in more than 30 patients treated with therapeutic doses of almitrine for at least 3-month were considered. Hence, the MAH has selected a total of 11 clinical studies of which:

- 7 were conducted with continuous daily administration of 100 to 200 mg of almitrine bimesylate,
- and 4 were conducted with a sequential schedule of administration using the maximal dose of 100mg daily and a therapeutic window of one month for every 2 months of treatment..

The critical assessment of the published studies is presented below.

### **Clinical studies with continuous administration**<sup>1234567</sup>

Among the 7 clinical studies with continuous daily administration of 100 to 200 mg of almitrine bismesylate, 2 were not controlled (Ansquier 1985, Marsac 1986) and 5 were controlled versus placebo (Arnaud 1983, Voisin 1987, Bardsley 1991, Bakran 1991, Gonzales 1994).

#### Not controlled studies (Ansquier 1985, Marsac 1986):

The MAH submitted data from 2 open label not controlled clinical studies with continuous administration:

1. Ansquer and al (Ansquer, 1985): not controlled study conducted from September 1980 to March 1983 in 17 centers located in France.
2. Marsac (Marsac, 1986): not controlled study conducted in 79 centers located in France.

These studies are summarised below (Table 4).

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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., Ivcevic A., Todoc 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)

**Table 4.** Clinical studies open label not controlled with continuous administration.

Reference of the publication	Daily dose (non sequential schedule)	Duration of continuous treatment	Number of patients included (N)/who completed the study	Nb of withdrawals n/N (%)
<b>ANSQUER, 1985</b>	100 mg	12 months	108/86	22/108 (20 %)
<b>MARSAC, 1986</b>	100-150 mg	6 months	556/415	141/556 (25 %)

The results of these studies are summarised below:

1. Ansquer and al (Ansquer, 1985):

In this study there was an increase in mean PaO<sub>2</sub> from baseline i.e.: + 5.5 mmHg at Month 6 and + 6.0 mmHg at Month 12, weak improvement in dyspnea and in PaCO<sub>2</sub> and RBC, with oral almitrine 100mg per day. However, any conclusion from this study should be cautious. Indeed, drop out rate was 20% = 22/108 before 12 months including reasons linked to progressive respiratory diseases (10 cases with deaths in 5 cases). The publication doesn't specify whether any method of imputation for missing data were applied. Moreover, this study was open labelled and not controlled. almitrine was combined with the conventional treatment which the patient was taking and it could be modified during the course of the study.

2. Marsac (Marsac, 1986):

In this study there was an increase in mean PaO<sub>2</sub> of + 5.7 mmHg at Month 3 and + 7 mmHg at Month 6, slight decrease in PaCO<sub>2</sub> and RBC, no effect on dyspnoea and on respiratory function with oral almitrine 100mg or 150 mg per day continuously. The publication doesn't specify the number of patients receiving 100 mg and those receiving 150 mg per day.

Any conclusion from this study should be cautious as this study was open and not controlled.

Moreover, almitrine was combined with the conventional treatment the patient was taking and it could be modified during the course of the study. The change in treatment during the treatment is not detailed nor analysed in the publication. This may have induced bias.

Also, drop out rate was high: 141/556 = 25%. The article presented the efficacy results on the per protocol population completing the 6 months trial i.e. 75% of the included population. Reasons for drop out are detailed in the publication as: 31 were related to adverse effects of the treatment (including 4 cases of increased dyspnoea), 16 deaths of cardiovascular origin (sudden death, cerebral haemorrhage, cerebrovascular accident, myocardial infarction, suicide etc.), 65 cases lost of follow-up, 14 miscellaneous cases, and for the 15 other cases no information are provided in the article.

Placebo controlled studies (Arnaud 1983, Voisin 1987, Bardsley 1991, Bakran 1991, Gonzales 1994).

The MAH submitted data from 5 controlled clinical studies with continuous administration:

1. Arnaud and al (Arnaud, 1983): placebo-controlled study conducted in 13 centers located in France.
2. Voisin and al: Vectarion International Multicenter Study (VIMS) (Voisin, 1987): placebo-controlled study set up in 1983 in multiple centres located in Europe, sponsored by the MAH.
3. Bakran and al (Bakran, 1990): multicenter study conducted in Yugoslavia, Slovenia, Croatia and Serbia.
4. Bardsley and al (Bardsley, 1991): Extension of VIMS study. Four of the European centres participating in the VIMS study (i.e. 1 in UK and 3 in Belgium), invited their patients to

continue in the same double blind placebo controlled manner for a further 12 months to provide a total follow-up of 24 months

5. Gonzalez and al (Gonzalez, 1994): monocenter study conducted in Spain (Madrid).

These studies are summarised below (Table 5).

**Table 5.** Placebo controlled clinical studies\_with continuous administration.

Reference of the publication	Daily dose (non sequential schedule)	Duration of continuous treatment	Number of patients included (N)/who completed the study	Nb of withdrawals n/N (%)
<b>ARNAUD, 1983 (Fr)</b>	200 mg/day during 3 months followed by 100 mg/day during 3 months	6 months	200/163 Almitrine : 100/84 Placebo : 100/79	37/200 (18.5%) A: 16/100 (16 %) P: 21/100 (21 %)
<b>VOISIN, 1987 (VIMS) (Eu)</b>	100-200 mg/day (increase the dose in case of no improvement of PO <sub>2</sub> > 5 mmHg at Months 3 and.or 6)	12 months	701/472 Almitrine : 344/205 Placebo : 357/267	229/701 (33%) A: 139/344 (40.4 %) P: 90/357 (25.2 %)
<b>BARDSLEY, 1991 (1)* (UK)</b>	100-200 mg/day ((increase the dose in case of no improvement of PO <sub>2</sub> > 5 mmHg at Months 3 and.or 6)	24 months	89/38 Almitrine : 43/14 Placebo : 46/24	51/89 (57%) A: 29/43 (67 %) P: 22/46 (48 %)
<b>BAKRAN, 1990 (YU, SL, Croatie)</b>	100 mg/day	3 months	40/35 Almitrine : 23/19 Placebo : 17/16	5/40 (12.5%) 4/23 (17 %) 1/17 (6 %)
<b>GONZALEZ, 1994 (SP)</b>	1 mg/kg/day (50-100 mg) (+ oxygen therapy)	3 months	65/52 Almitrine : 33/28 Placebo : 32/24	5/33 (15 %) 8/32 (25 %)

\* Sub group of VIMS study (Voisin 1987) for the 12 first months of treatment.

**Table 6.** Results on the placebo controlled clinical studies\_with continuous administration.

Study	Design	Treatment per day	Number of subjects Entered/ Completed	Duration	Inclusion criteria	Results Almitrine vs. placebo
<b>ARNAUD and al, 1983</b>	Randomised Double blind Parallel group Versus placebo	200mg for 3 months then 100mg for 3 months	200/ 163 Almitrine: 100/ 84 placebo: 100/ 79	6 months	COPD patients PaO <sub>2</sub> ≤ 70 mmHg PaCO <sub>2</sub> ≥ 43 mmHg FEV <sub>1</sub> ≤ 70%	PaO <sub>2</sub> : +6.9mmHg (M3) +5.2 mmHg (M6, p<0.001) PaCO <sub>2</sub> : -4.3mmHg (M3) -3.9mmHg (M6, p<0.01) Dyspnoea score decrease (p<0.001) RBC decrease when polycythaemia (p<0.001) Hospitalisations for acute exacerbation decrease (18% almitrine vs. 33% placebo, p<0.001)
<b>VOISIN and al,, 1987</b>	Randomised Double blind Parallel	100 a 200 mg	701/ 472 Almitrine: 344/ 205	12 months	COPD patients 45 ≤ PaO <sub>2</sub> ≤	PaO <sub>2</sub> : +6.3 mmHg (p<0.001). PaCO <sub>2</sub> : -2.3 mmHg

	group Versus placebo		placebo: 357/ 267		65 mmHg 35 ≤ PaCO <sub>2</sub> ≤ 60 mmHg FEV1 ≤ 70%	(p<0.001) Dyspnea scale score: NS changes 6MWT: NS changes FEV1: slight improvement (p<0.001) RBC decrease (p<0.001) Hospitalisations and right heart failure reduction (p<0.05) Weight decrease: - 4.2 kg
<b>BAKRAN and al 1990</b>	Randomised Double blind Parallel group Versus placebo	100 mg	40/ 35 Almitrine: 23/ 19 placebo: 17/ 16	3 months	COPD patients 45 ≤ PaO <sub>2</sub> ≤ 65 mmHg 35 ≤ PaCO <sub>2</sub> ≤ 60 mmHg FEV1 ≤ 70%	PaO <sub>2</sub> : +5.0 mmHg (p<0.01). PaCO <sub>2</sub> : - 2.4 mmHg (p<0.05) Dyspnea scale score: improved (p<0.001) 6MWT: improved (p<0.001) Lung function: NS changes
<b>BARDSLEY and al, 1991</b>	Randomised Double blind Parallel group Versus placebo	100-200 mg	89/ 38 Almitrine: 43/ 14 placebo: 46/ 24	24 months	Follow-up of Voisin study	PaO <sub>2</sub> : +5.6 mmHg (p<0.001). PaCO <sub>2</sub> : -1.9 mmHg (p<0.001)
<b>GONZALEZ and al, 1994</b>	Randomised Double blind Parallel group Versus placebo	50-100 mg LTOT	65/ 52 Almitrine: 33/ 28 placebo: 32/ 24	3 months	COPD patients PaO <sub>2</sub> < 55 mmHg FEV1 < 80%	PaO <sub>2</sub> : +4.93 mmHg (p<0.01). PaCO <sub>2</sub> : -1.2 mmHg (NS)

### Double blinded placebo controlled clinical studies with sequential administration<sup>8,9,10,11, 12</sup>

Originally suggested doses of continuous administration of almitrine (50-200mg per day) were found to occasionally result in a steady increase in almitrine plasma levels as a result of the long half-life of almitrine bismesylate. This was suspected to be the main causes of side effects, notably of peripheral neuropathies (paraesthesia) and weight loss (Voisin, 1987). Moreover PaO<sub>2</sub> was found to be related to almitrine plasma level only for the range 200-300 ng/ml. Higher almitrine plasma levels were not related to higher PaO<sub>2</sub> response (Voisin, 1987).

<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> Sans-Torres J., Domingo C., Moron A., Rué M., Marin A.. long term effects of almitrine bismesylate in COPD patients with chronic hypoxaemia. Respir Med 2003; 97: 599-605 (PE10387)

<sup>12</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)

Consequently, further studies aimed at stabilising almitrine plasma levels around 300 ng/ml, were performed using a therapeutic window of one month for every 2 months of treatment and lower daily doses.

The MAH submitted a total of 4 clinical studies that were conducted with this sequential administration and controlled versus placebo:

1. Weitzenblum and al (Weitzenblum, 1992): multicentre placebo-controlled study conducted from January 1986 to November 1988 in 14 centres located in France (randomised double blind parallel group versus placebo).
2. Bardsley and al (2) (Bardsley, 1992): multicentre study in several centres located in the United Kingdom (randomised double blind parallel group versus placebo), sponsored by the MAH.
3. Nowak and al (Nowak, 1998): multicentre study conducted in 9 centres in Germany (randomised double blind parallel group sequential vs continuous vs placebo).
4. Zielinski/ Gorecka (Gorecka, 2003): multicentre study conducted in 11 centres in Poland (randomised double blind parallel group versus placebo).

An additional publication - Sans Torres and all (2003) - was considered by the PRAC during assessment. This study was conducted between September 1995 and September 1999 in Barcelona (Spain) independently of the MAH.

These studies are summarised below (Table 7).

**Table 7.** Double blinded, placebo controlled clinical studies (sequential schedule).

Reference of the publication	Daily dose with sequential treatment	Duration of treatment	Number of patients included (N)/completed the study	Nb of withdrawals n/N (%)
<b>WEITZENBLUM, 1992, (Fr)</b>	100 mg/day	12 months	102/62 Almitrine : 65/37 Placebo : 37/25	28/65 (43 %) 12/37 (32 %)
<b>BARDSLEY, 1992 (2) (UK)</b>	< 50 kg : 50mg/day 50 à 64 kg : 75 mg/day > 60kg : 100 mg/day	6 months	85/64 Almitrine : 50/36 Placebo : 35/28	14/50 (28%) 7/35 (20 %)
		Extension : 6 month : almitrine en ouvert, suivi de 6 month sans traitement	36/27	
<b>NOWAK, 1998 (DE)</b>	100mg/day sequential versus 75 mg/day continue	6 months	64/36 Almit sequentiel: 23/11 Almit continu: 21/7 Placebo : 20/18	12/23 (52 %) 14/21 (67 %) 2/20 (10 %)
<b>GORECKA, 2003 (PL)</b>	100 mg/day	12 months	115/77 Almitrine :57/34 Placebo : 58/43	23/57 (40 %) 15/58 (26 %)
<b>SANS-TORRES, ** 2003 (SP)</b>	< 75 kg = 50mg/day ≥ 75 kg = 100mg/day	12 months	81/42 Almitrine : 41/18 Placebo: 40/24	39/81 (48%) 23/41 (56%) 16/40 (40%)

- *Sequential schedule* : One months was out after the third, the sixth and the ninth months



The results of these studies are summarised below (Table 8).

**Table 8.** Results on the double blinded, placebo controlled clinical studies (sequential schedule).

Study	Design	Treatment per day	Number of subjects Entered/ Completed	Duration	Inclusion criteria	Results Almitrine vs. placebo
<b>WEITZEN BLUM, 1992).</b>	Randomised Double blind Parallel group Versus placebo	100 mg/d sequential	102/ 62 Almitrine: 65/ 48 placebo: 37/ 32	12 months	COPD patients 45 ≤ PaO <sub>2</sub> ≤ 65 mmHg 35 ≤ PaCO <sub>2</sub> ≤ 60 mmHg FEV <sub>1</sub> ≤ 70% 25 ≤ FEV <sub>1</sub> /VC ≤ 65%	PaO <sub>2</sub> : +6.7 mmHg, p<0.001 PaCO <sub>2</sub> : -1.2 mmHg (NS) Dyspnoea score: no changes vs. slight increase (NS) Lung function test: NS changes LTOT use: < than placebo (p<0.05) Weight decrease: -1.4 kg
<b>(BARDSL EY, 1992).</b>	Randomised Double blind Parallel group Versus placebo	50 to 100 mg/d sequential	85/ 64 Almitrine: 50/ 36 placebo: 35/ 28	6 months	COPD patients 50 ≤ PaO <sub>2</sub> ≤ 65 mmHg 35 ≤ PaCO <sub>2</sub> ≤ 60 mmHg FEV <sub>1</sub> ≤ 0,6 L	PaO <sub>2</sub> : + 5,9 mmHg, p<0.001 PaCO <sub>2</sub> : -1.1 mmHg (NS) Dyspnoea visual scale > than placebo (p<0.05) 6MWT: > than placebo (p<0.05) Lung function test NS changes Weight decrease: -3.6 kg (p<0.001)
	Open study	50 to 100 mg/d	36/ 27	12 months	+ 6months follow-up	PaO <sub>2</sub> : +7.0 mmHg, p<0.001)
<b>NOWAK and al, 1998</b>	Randomised Double blind Parallel group Sequential vs continuous vs placebo	100 mg/d sequential	64 Almitrine seq: 23/ Almitrine seq: 21/ placebo: 20/	8 months	COPD patients	
<b>GORECKA and al, 2003</b>	Randomised Double blind Parallel group Versus placebo	100 mg/d sequential	115/ 77 Almitrine: 57/ 34 placebo: 58/ 43	12 months	COPD patients 56<PaO <sub>2</sub> ≤ 65 mmHg FEV <sub>1</sub> ≤ 70% 25<FEV <sub>1</sub> /VC ≤ 70%	PaO <sub>2</sub> : +3,2 mmHg (p=0.003). PaCO <sub>2</sub> : -2.92 mmHg (NS) Dyspnoea score: no changes FEV <sub>1</sub> : no changes

#### Sans Torres and all (2003)

The Sans Torres and all 2003 publication was provided by Members States during the assessment.

This study failed in demonstrating satisfactory improvement in blood gasometry or in any other criteria of efficacy with almitrine.

In this study none of the efficacy parameters studied (PaO<sub>2</sub>, PaCO<sub>2</sub>, pulmonary function, 6 MWT, nocturnal oxymetry, quality of life) was modified with almitrine administered at 1 mg/kg/day in an intermittent schedule during 12 months. Almitrine did not improve blood gas in the 12 month follow-up, nor in any of the measurements performed after 3, 6, 9 months. This study also failed to find a subgroup of patients with improved PaO<sub>2</sub>. Neither oxygen therapy nor the degree of hypercapnia at the beginning of the study modified the evolution of PaO<sub>2</sub>. Similar rate of responders was found in the placebo and almitrine groups.

This study was the first to evaluate the effect of almitrine on patient's quality of life. No difference was observed as compared to placebo. As stated by the authors, this would suggest that almitrine was well tolerated in the study but there were no demonstrable clinical benefits.

There was no statistical difference in terms of use of LTOT.

In this study, the dropout rate at Month 12 was higher in the almitrine group: 23 /41 = 56 % as compared to the placebo group 16/40 = 40 % (total drop-out: 39/81 = 48%).

The authors concluded that, in line with the low prescription of this drug in daily clinical practice by pulmonologist treating patients with chronic respiratory failure, almitrine does not seem to be an effective drug for long term treatment of hypoxemia related to COPD. almitrine is no more marketed in Spain.

### **Discussions on efficacy results**

The slight improvement in PaO<sub>2</sub> cannot be considered that this translates in a real benefit for the patients in terms of exercise capacity/quality of life and outcome of the disease/survival.

#### Effect on blood gas:

- Effect on PaO<sub>2</sub>:

Almitrine was able to slightly increase mean PaO<sub>2</sub> as compared to placebo groups in all published studies, except in Sans Torres and Nowack publications where no effect was shown as compared to placebo

The increase in mean PaO<sub>2</sub> values presented by the authors of the publications at the end of the studies were comprised between + 3.2 mmHg and + 7.0 mmHg,

Mean value presented on the per protocol population may have been overestimated bearing in mind the high and frequently unbalanced rates of drop out.

Changing the regime of drug administration from continuous to sequential dosing resulted in an equivalent effect on PaO<sub>2</sub> mean values reported at the end of the studies.

Only a proportion of patients showed a response in PaO<sub>2</sub>. Rate of responders defined as patients increasing their PaO<sub>2</sub> more than 5 mmHg was reported in some studies with varied values: 33%, 43%, 46%, 56%, 60%. The ability of almitrine to increase PaO<sub>2</sub> appeared variable with large differences in individual changes. The mechanism responsible for different reactions could not be established and the clinical profile of drug responders could not be defined. Individual responses in terms of blood gas tension improvement cannot be predicted from baseline physiological or clinical measurements but it appeared that more than a third of hypoxemic COPD patients did not respond to almitrine.

The results concerning efficacy with low doses and intermittent schedules of administration were somewhat contradictory. The negative results from Nowak and Sans Torres showed that if almitrine is

effective in improving oxygenation, its therapeutic range is narrow and doesn't appear under 1 mg/kg/day.

- Effect on PaCO<sub>2</sub>:

Results on PaCO<sub>2</sub> are controversial. The studies reported very moderate decrease in PaCO<sub>2</sub> and the differences as compared to placebo did not reach statistical significance with sequential treatment and at a dose of 100 mg per day. Some authors considered that the decrease in mean PaCO<sub>2</sub> in the almitrine group could also be to some extent ventilation dependent.

Effect on dyspnoea:

Results on dyspnea are controversial. Three of the publications (of which 2 with continuous treatment and one with sequential treatment) reported a slight effect on dyspnoea as assessed on visual analogue scale and no effect was observed on dyspnoea as compared to placebo in the other publications.

A higher rate of unexplained dyspnoea was reported in a series of 67 patients treated with oral almitrine 100 mg (9% of cases), 200 mg/day (19%) as compared to placebo (4 %) high doses of 200 mg per day of almitrine as compared to placebo in a study conducted in 67 patients (Bell RC 1986, not provided by the MAH for the purpose of the present review). Moreover, in the VIMS study (Voisin and all publication) using continuous high dose expiratory signs and symptoms, shortness of breath or awareness of respiration, were reported in the almitrine group. According to the authors, some individual patients found the increase of dyspnoea sufficiently distressing to withdraw. High doses of almitrine increased the ventilation rate.

Effect on exercise capacity:

Four publications referred to the assessment of exercise capacity using the 6 minute walk test (6MWT) compared to placebo (Voisin 1987, Bakran 1990, Bardsley 1992, Sans Torres 2003)

A difference was reported in 6 MWT as compared to placebo in Bakran 1990 publication. In this publication a mean increase of +93 m from baseline was reported after 3 months treatment in the 19 patients who completed the study among the 23 initially included (versus placebo : + 7 m in the 16 patients who completed the study among the 17 patients initially included). These results are from a small per protocol population only.

In Bardsley 1992 study, using sequential schedule, the mean 6MWT distance did not change in the 30 patients remaining in the almitrine group after 6 month treatment (while it decreased in the placebo group, the difference between the groups being statistically significant).

In the 2 other publications which referred to the 6 MWT, no difference could be shown in the almitrine group as compared to placebo (Voisin (ITT analysis), Sans Torres).

These data cannot support the benefit of almitrine on exercise capacity.

Effect on long term oxygen therapy (LTOT):

No studies allowed to demonstrate that long term oxygen therapy can be discontinued, delayed or even avoided with almitrine.

One publication (Gonzales 1994) referring to a clinical trial conducted with almitrine 1 mg/kg/day during 3 months aimed at assessing the effect of almitrine in a homogeneous group consisting exclusively of COPD patients on ambulatory oxygen. Seven patients (among 33 included) in the almitrine group and 2 patients (among 32 included) in the placebo group could stop ambulatory

oxygen but without the difference between the 2 groups being significant. They were follow-up for 9 months and remained without LTOT.

Studies conducted in a population consisting exclusively of patients not treated with LTOT with moderate hypoxemia could not demonstrate any benefit of almitrine with respect to the delay of initiation of LTOT as compared to placebo (Bardsley 1992-6 months, Goreka 2003-12 months, Novak 1998- 8 months).

Weitzenblum publication presented the percentage of patients using oxygen at the end of the 12 months study with almitrine as compared to placebo considering a stable status in almitrine group and increased rate of LTOT at the end of the study in the placebo group. However, the frequency was calculated on the per protocol population and this presentation do not appear to introduce bias as substantially commented above.

#### Effect on outcome of the disease:

Five publications referred to the estimation of the rate of hospitalisations and/or right heart failures.

Two of them (Arnaud, 1983 and Voisin, 1987) using almitrine continuously at the doses of 100-200 mg during 6 and 12 months respectively, reported a significantly lower rate in hospitalisations as compared to placebo. However, Arnaud publication doesn't provide any information on the reasons for hospitalisations nor on the rate of right heart failures in each group. In the Voisin publication drop out rate was important and predominant in the almitrine group. The authors considered that the lower rate of episodes of right heart failure in the almitrine group could have been related to the loss of weight observed in the almitrine group and especially in overweight patients. Weight loss is identified as an unexplained but concerning adverse effect (see safety discussion). Noticeably, the rate of withdrawals in this study due to deterioration of respiratory disease including deaths was slightly higher in the almitrine group than in the placebo group (predominantly in non-LTOT group while no difference was observed when patients used LTOT).

In the 2 other publications describing the outcome in terms of hospitalisation/exacerbations i.e. Bardsley 1992 and Goreka 2003, no differences were reported between the almitrine and placebo groups over the 6 and 12 months sequential treatment durations, respectively.

#### Effect on survival:

Only one publication estimated the survival at 24 months (Bardsley 1991) in 89 patients with COPD. Almitrine was used continuously with daily doses of 100-200 mg. Among them 38 patients completed the 24 month follow-up: 14/43 patients in the almitrine group and 24/46 in the placebo group. At month 24, death rates were reported as 16.2% (7/43 patients) in the almitrine group and 13% (6/46 patients) in the placebo group. Based on Kaplan Meyer estimates, the authors stated that there was no statistically significant difference in survival after 2 years in patients in the almitrine group (82%) as compared to those on the placebo group (86%). However, the apparent tendency cannot be considered as in favour of almitrine.

#### Effect on quality of life:

Only Sans Torres publication studied the effect of almitrine on patient's quality of life (Chronic Respiratory Disease Questionnaire, Guyatt). No effect could be found with almitrine as compared to placebo.

### **Conclusion on efficacy**

In view of the 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 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.

## **3. Overall discussion and risk/benefit assessment**

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 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.

## 4. Communication plan

The PRAC considered that a Direct Healthcare Professional Communication (DHPC) was needed to communicate on the review of almitrine and the recommended regulatory measures.

Relevant European healthcare professional organisations were consulted and provided input on the draft DHPC. The final version of this DHPC agreed by the PRAC is provided together with the communication plan.

The MAH should agree the translations and local specificities of the DHPC with national competent authorities. The DHPC should be sent to physicians and pharmacists.

## 5. Conclusion and grounds for the 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.