HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

22 June 2011

Review of the dossier for the proprietary medicinal product listed for five years from 2 July 2006 (*Journal Officiel* dated 3 October 2007).

VECTARION 50 mg, scored film-coated tablets
B/30 (CIP code: 326 137-9)

Applicant: SERVIER

Almitrine bismesylate
ATC Code: R07AB07

Date of Marketing Authorisation: 10 December 1982
Dates of main amendments to the Marketing Authorisation:

- 2 May 1986 (introduction of sequential dosage regimen)
- 11 September 2003 (clarifications concerning the sequential dosage regimen and patients with renal failure, and of contraindications, warnings and precautions for use related to peripheral neuropathy)

Reason for request: Renewal of inclusion on the list of medicines refundable by National Health Insurance.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Almitrine bismesylate

1.2. Indications

"Respiratory insufficiency with hypoxaemia related to chronic obstructive pulmonary disease."

1.3. Dosage

"The dosage is 50 to 100 mg (1 to 2 tablets daily), divided into two doses during main meals.
After a 3 months initial treatment, the sequential regimen should be used, i.e. one month off treatment for every two months on treatment
It may be necessary to adjust treatment depending on the patient's weight and/or any side effects:

- Depending on the patient's weight: in patients weighing less than 50 kg, a single daily 50 mg tablet is recommended,
- Depending on any undesirable effects: (see SPC section 4.4. *Warnings and special precautions for use*).

Patients with renal impairment:
There is no need to adjust the dosage in patients with renal impairment.

Administration of VECTARION is compatible with concomitant oxygen therapy."

2 REMINDER OF THE COMMITTEE'S OPINIONS AND CONDITIONS OF INCLUSION

Committee Opinions of 27 April 1983, 11 September 1985, 15 February 1989 and 26 May 1993:
This is a novel substance whose main property is to increase the quantity of circulating oxygen, while the quantity inhaled remains unchanged.
The Committee had issued an opinion recommending listing and maintenance of listing of VECTARION in all the clinical indications in the Marketing Authorisation.

Committee Opinion of 4 February 1998:
In view of the fact that VECTARION results in improved blood gas levels, and that the sequential regimen has reduced its adverse effects (notably peripheral neuropathy) and that there is no alternative form of treatment, under these conditions, the therapeutic role of VECTARION is recognised for patients with hypoxia before oxygen therapy.

Committee Opinion of 23 March 2000:
Re-assessment of actual benefit of medicinal products refundable by National Health Insurance.
The level of actual benefit for the proprietary medicinal product VECTARION 50 mg, film-coated tablets, is substantial.
This actual benefit refers to use of the proprietary medicinal product only in patients with PaO_2 between 55 and 65 mmHg.

Committee Opinion of 4 April 2001:

The actual benefit for the proprietary medicinal product VECTARION 50 mg, film-coated tablets, is substantial.

This actual benefit refers to use of the proprietary medicinal product only in patients with PaO_2 between 55 and 65 mmHg.

The transparency Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance.

Committee Opinion of 04 July 2007:

COPD causes incapacity and marked degradation of quality of life and may be life-threatening.

Almitrine has been shown to have a positive effect on PaO_2. However, this effect is small and almitrine is not recommended in any clinical situation as it has not contributed any response to the aims of treatment for COPD, which are to:

- reduce symptoms
- prevent disease progression
- improve exercise tolerance
- improve quality of life
- prevent and treat complications and exacerbations
- reduce COPD-related mortality

The efficacy/tolerance ratio is low.

An alternative medical therapy exists, oxygen therapy, when hypoxaemia (between 55 and 60 mmHg) is associated to polycythaemia or clinical signs of chronic cor pulmonale or pulmonary artery hypertension or nocturnal arterial desaturation without apnoea.

The actual benefit for the proprietary medicinal product VECTARION 50 mg, film-coated tablets, is low.

The transparency Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance.

3 SIMILAR MEDICINAL PRODUCTS

3.1. ATC Classification (2011)

R	:	Respiratory system
R07	:	Other respiratory system products
R07A	:	Other respiratory system products
R07AB	:	Respiratory stimulants
R07AB07	:	Almitrine

3.2. Medicines in the same therapeutic category

VECTARION is the only medicine in its pharmacotherapeutic category with an indication in chronic respiratory failure with hypoxaemia related to chronic obstructive pulmonary disease.

3.3. Medicines with a similar therapeutic aim

Oxygen therapy is indicated to correct hypoxia of various origins and requiring normobaric or hyperbaric oxygen therapy.

4 UPDATE ON DATA MADE AVAILABLE SINCE THE PREVIOUS OPINION

4.1. Efficacy

No new clinical data have been submitted since the previous Transparency Committee Opinion (4 July 2007).

The efficacy of VECTARION 50 mg was originally assessed in six randomised, double-blind, placebo-controlled trials in patients with COPD with hypoxaemia (see table of principal characteristics below).[1,2,3] The summary will only include results of trials using the sequential dosage regimen, corresponding to the current Marketing Authorisation.

[1] Weitzenblum E, Arnaud F et Bignon J et al. *Administration séquentielle d'une posologie réduite d'almitrine à des malades BPCO* [Sequential administration of a reduced dosage of almitrine in patients with COPD]. Controlled multicentre trial Rev Mal Resp 1992; 9: 455-63

[2] Bardsley PA, Howard P, De Backer W, Vermeire P, Mairesse M, Ledent C, Radermecker M. Two years treatment with almitrine bismesylate in patients with hypoxic chronic obstructive airways disease Eur Respir J 1991; 4: 308-10

[3] Gorecka D, Sliwinski P, Palasiewicz G, Pachocki, Zielinski J and the Almitrine Study Group Effects of almitrine bismesylate on arterial blood gases in patients with chronic obstructive pulmonary disease and moderate hypoxaemia. Resp 2003; 70: 275-283

Main characteristics of available clinical trials studying the efficacy of almitrine:

Author	Aims	Duration	Patients	Patients recruited	Dosage regimen for almitrine	Efficacy outcome endpoints
Weitzenblum (1988)	Efficacy of sequential administration of almitrine.	1 year	- COPD - FEV_1< 70% of predicted value - 25% ≤ FEV_1/FVC≤ 65% - 45 mmHg ≤ PaO_2 ≤ 65 mmHg - 35 mmHg ≤ $PaCO_2$ ≤ 60 mmHg	n=102	50 mg twice-daily in sequential regimen (2 months on treatment / 1 month off treatment)	Dyspnoea, blood gas analysis, respiratory function tests.
Bardsley (1991)	Efficacy of reduced doses of almitrine in COPD with hypoxaemia.	Almitrine or placebo for 6 months followed by almitrine for 6 months	- FEV_1>0.6 L - 50 mmHg ≤ PaO_2 ≤ 65 mmHg - 35 mmHg ≤ $PaCO_2$ ≤ 60 mmHg	n=85	0-6 months: 50-100 mg/day in sequential regimen (2 months on treatment / 1 month off treatment) 6-12 months: sequential regimen (2 months on treatment / 1 month off treatment)	Dyspnoea, hospital admissions, episodes of superinfection, blood gas analysis, respiratory function tests
Zielinski (1998)	To confirm that almitrine, in a sequential regimen, prevents or at least slows down the decline in PaO_2 in patients with COPD with hypoxaemia, and to study the effect on $PaCO_2$.	1 month pre-inclusion followed by 12 months' treatment	- COPD stable during pre-inclusion period - FEV_1 < 70% of predicted value - 25% ≤ FEV_1/FVC ≤ 70% - 55 mmHg ≤ PaO_2 ≤ 65 mmHg	n=128 preselected n=115 randomised	Pre-inclusion: placebo 12 months' treatment with almitrine or placebo in sequential regimen 3 months on treatment/1 month off treatment followed by 2 months on treatment/1 month off treatment up to 12 months	Primary efficacy endpoint: PaO_2 in ambient air at M0, M3, M6, M9 and M12 Secondary endpoint: $PaCO_2$, respiratory function tests, dyspnoea

Study results:

Weitzenblum (1988):
After 12 months' treatment there was no significant difference between almitrine and placebo for dyspnoea score, $PaCO_2$, forced expiratory volume in 1 second (FEV_1), vital capacity (VC) or FEV_1/FVC ratio.
Almitrine was superior to placebo (p=0.003) for PaO_2 which increased from 59.1±0.7 to 65.8±1.6 mmHg under almitrine and from 58.4±1.2 to 60.2±1.8 mmHg under placebo.

Bardsley (1991):
In this trial, almitrine was used at a reduced dose in a sequential regimen.
After six months' treatment, dyspnoea measured on a visual analogue scale (VAS) and by the six minute walk test remained stable in the almitrine group but deteriorated in the placebo group. The difference observed between the groups for these two criteria was significant.

	Almitrine		**Placebo**		p
Dyspnoea:	Baseline value	6 months	Baseline value	6 months	
VAS (mm)	23.4 ± 18.4	22.1 ± 18.9	19.8 ± 21.2	30.7 ± 24.2	<0.05
Walk test (m)	305 ± 90	305 ± 105	318 ± 102	279 ± 97	<0.05

FEV_1 and forced vital capacity (FVC) did not improve under either almitrine or placebo.

PaO_2 increased from 58.8±5.5 to 64.7±10.4 mmHg under almitrine, while it remained unchanged under placebo. The difference observed between the groups was significant (p<0.01).
$PaCO_2$ remained stable in both groups.

Zielinski (1998):
After 12 months' treatment, change in PaO_2 in ambient air (primary efficacy criteria) was 3.2±6.6 mmHg under almitrine compared with -0.15±6.3 mmHg under placebo. The difference observed between treatments (3.4 mmHg, 95% CI = [1.4; 5.3]) was statistically significant (p=0.003) but did not reach the threshold for clinical significance defined beforehand (5 mmHg).

There was no significant difference between almitrine and placebo for the other endpoints of $PaCO_2$, PaO_2 in response to the oxygen test, spirometry or dyspnoea.

4.2. Adverse effects/Safety

The current SPC states that peripheral neuropathy and/or weight loss have been observed with long-term treatment with almitrine (more than one year). Treatment should be discontinued in the event of weight loss or symptoms indicating paraesthesia, such as tingling, pins and needles, persistent numbness in the legs.

The other adverse effects mentioned in the SPC are nausea, epigastric burning and heaviness, dyspepsia, transit disorders, insomnia, drowsiness, agitation, anxiety, palpitations, dizziness, and awareness of respiratory movements. These undesirable effects are classified as rare.

No adverse effects not mentioned in the SPC were identified in the PSUR covering the years 1997 to 2006 and 2007 to 2010.

4.3. Conclusion

Among the clinical data available on the use of VECTARION in a sequential dosage regimen and already reviewed by the Transparency Committee, three placebo-controlled studies (randomised, double-blind) assessed the efficacy of almitrine in patients with stable COPD with hypoxaemia. Under this type of dosage regimen, almitrine improved PaO_2 by about 3-5 mmHg as compared to placebo and in one of the three studies it improved dyspnoea (by about 10 mm on a VAS and 40 m in a 6 - min walk test). In contrast, it was not found to be superior to placebo for $PaCO_2$ or spirometry parameters.

The efficacy of almitrine was therefore only demonstrated for reducing hypoxaemia, but this effect was small. No benefit was demonstrated against clinical manifestations (dyspnoea, hospital admissions for decompensation, exacerbations requiring antibiotic therapy), nor for spirometry parameters apart from PaO_2. Effects on quality of life, time to starting oxygen therapy and mortality were not studied.

The change of dosage regimen to a sequential regimen reduced the frequency of occurrence of peripheral neuropathy, which is however a serious effect. These adverse effects were considered by the National Pharmacovigilance Committee to have become rare.

5 DRUG USAGE DATA

According to IMS-DOREMA data (moving annual total 2011), VECTARION was the subject of 20,000 prescriptions.

6 TRANSPARENCY COMMITTEE CONCLUSIONS

6.1. Re-assessment of actual benefit

COPD causes incapacity, marked degradation of quality of life and may be life-threatening.

This proprietary medicinal product is used as symptomatic therapy.

Public health benefit:

The public health burden of COPD is major.

Improvement in the treatment of COPD is a public health need which is an established priority (French 2004 Law on Public Health,[4] GTNDO[5]). For symptomatic treatment of COPD, the therapeutic need is covered by existing symptomatic therapies.

The available clinical data do not demonstrate any impact in terms of morbidity or mortality or quality of life for the proprietary medicinal product VECTARION as compared to existing therapies.

This proprietary medicinal product is therefore not able to satisfy an identified public health need.

Consequently, the proprietary medicinal product VECTARION has no public health benefit.

The efficacy/tolerance ratio is moderate.

[4] Law on Public Health 2004: Law no. 2004-806 of 09 August 2004 concerning public Health policy: objective no. 75 [rapport_DREES_indicateurs - July 2005]

[5] *Groupe Technique National de Définition des Objectifs* [French National Health Executive Technical Group for Defining Objectives] (DGS-2003)

An alternative therapy exists, i.e. oxygen therapy.

According to the most recent guidelines (GOLD, updated 2010 and SPLF, updated 2009), almitrine no longer has a role in the treatment strategy.

Consequently, the actual benefit of VECTARION 50 mg, film-coated tablets, is insufficient to allow reimbursement by National Health Insurance.

6.2. Therapeutic use

6.2.1. Treatment strategy

Diagnosis of COPD and management of patients should include an assessment of stage of severity of COPD based on a review of symptoms (chronic cough, dyspnoea on exertion, production of purulent sputum, exacerbations) and respiratory function tests.

The aims of treatment for COPD are to reduce symptoms, prevent disease progression, improve exercise tolerance, improve quality of life, prevent and treat complications and exacerbations and reduce COPD-related mortality. Improvement of PaO_2 (transient and reversible on withdrawal of treatment) is not one of the main treatment objectives in COPD.

No medicines prevent progress of COPD to chronic respiratory failure. Quitting smoking is the only measure likely to re-establish a pattern of normal decline in FEV_1. Anti-flu vaccine is indicated. Rehabilitation with exercise and respiratory physiotherapy helps to improve symptoms, quality of life and participation in activities of daily living.

Drug therapy for stable COPD (other than during exacerbations) should be adjusted stepwise depending on stage of severity and response to treatment. The medicines used are intended to reduce symptoms and reduce the frequency and severity of exacerbations.

Bronchodilators, beta-2 agonists and inhaled anticholinergics are the main forms of symptomatic treatment for COPD. Short-acting inhaled bronchodilators (beta-2 agonists or anticholinergics), taken as needed, are the recommended first-line therapy.
Long-acting bronchodilators are recommended when continuous symptomatic therapy is required, i.e. when dyspnoea persists despite the use of a short-acting bronchodilator several times a day.
Three long-acting beta-2 agonists (formoterol, salmeterol and indacaterol) and a long-acting anticholinergic (tiotropium) are available. Their efficacy is similar.
These three medicines are used as continuous first-line symptomatic therapy for COPD.

Long-acting theophylline may be used if the patient has problems using inhaled bronchodilators or if the latter achieve inadequate improvement in dyspnoea; their use is restricted by their narrow therapeutic range.

Inhaled corticosteroids may only be used in conjunction with a long-acting bronchodilator in patients with severe COPD with $FEV_1 < 50\%$ theoretical value and repeated exacerbations. They have not demonstrated any effect on mortality (all-cause mortality) and they increase the risk of lower respiratory tract infection, particularly pneumonia.

Treatment with a long-acting bronchodilator or with a combination of long-acting bronchodilator and inhaled corticosteroid should only be continued if they are found to have a beneficial effect on symptoms.
Systemic corticosteroids are not recommended.

Oxygen therapy is restricted to patients with COPD when, some time after an acute episode, and provided they are receiving optimum treatment (i.e. a combination of quitting smoking,

bronchodilators and physiotherapy), measurement of blood gases in ambient air performed on two occasions has shown:

- either PaO_2 of 55 mmHg or lower;
- or PaO_2 between 56 and 59 mmHg, combined with one or more of the following signs:
  - polycythaemia (haematocrit > 55%);
  - clinical signs of chronic cor pulmonale;
  - pulmonary artery hypertension (mean pulmonary artery pressure 20 mm Hg or more);
  - nocturnal arterial desaturation without apnoea, irrespective of $PaCO_2$ level.

Oxygen therapy is the only treatment for which there is evidence of efficacy on survival and quality of life in patients with chronic respiratory failure.

6.2.2. Therapeutic use

Almitrine is no longer mentioned in the guidelines (GOLD 2010, SPLF 2009 consensus), and no longer has a role in the management of COPD.

6.3. Transparency Committee recommendations

The transparency Committee recommends that the product should not continue to be included on the list of medicines refundable by National Health Insurance or on the list of medicines approved for hospital use.

The Transparency Committee recommends that the product should be removed from the list of medicines refundable by National Health Insurance and from the list of medicines approved for hospital use.