HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

16 July 2008

VOLIBRIS 5 mg, film-coated tablets
Box of 30 (CIP: 386 578 -1)

VOLIBRIS 10 mg, film-coated tablets
Box of 30 (CIP: 386 580 -6)

Appliquant : GLAXOSMITHKLINE

ambrisentan

ATC code : C02KX02

List I
Medicinal product for hospital prescription only, restricted to doctors and/or departments specialising in pneumology, cardiology or internal medicine.
Medicinal product requiring specific monitoring during treatment.

Date of Marketing Authorisation (centralised procedure): 21 April 2008

Reason for request: Inclusion on the list of medicinal products approved for use by hospitals.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

ambrisentan

1.2. Indications

VOLIBRIS is indicated for the treatment of patients with pulmonary arterial hypertension (PAH) classified as WHO functional class II and III[1], to improve exercise capacity . Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease.

1.3. Dosage

Treatment must be initiated by a physician experienced in the treatment of PAH.
VOLIBRIS is to be taken orally at a dose of 5 mg once daily. It is recommended that the tablet is swallowed whole and it can be taken with or without food.
Some additional efficacy has been observed with 10 mg VOLIBRIS in patients with class III symptoms, however an increase in peripheral oedema has also been observed. Patients with PAH associated with connective tissue disease may require 10 mg VOLIBRIS for optimal efficacy. Confirm that the 5 mg dose is well tolerated before considering an increase in dose to 10 mg VOLIBRIS in these patients
Limited data suggest that the abrupt discontinuation of VOLIBRIS is not associated with rebound worsening of PAH.
When co-administered with cyclosporine A, the dose of ambrisentan should be limited to 5 mg once daily and the patient should be carefully monitored.

Children and adolescents
VOLIBRIS is not recommended for use in patients below 18 years of age due to a lack of data on safety and efficacy.

Elderly
No dose adjustment is required in patients over the age of 65.

Patients with renal impairment
No dose adjustment is required in patients with renal impairment (see section 5.2). There is limited experience with VOLIBRIS in individuals with severe renal impairment (creatinine clearance <30 ml/min); initiate therapy cautiously in this subgroup and take particular care if the dose is increased to10 mg VOLIBRIS.

[1] The NYHA classification (New York Heart Association Functional Classification) is based on the patient's functional capacity. It divides patients into four classes:
- Class I: no limitation of physical activity. No dyspnoea or fatigue when undertaking activities of daily living
- Class II: slight limitation of physical activity. Discomfort when undertaking strenuous physical activity. No discomfort at rest.
- Class III: clear limitation of physical activity. Discomfort when undertaking even moderate activities of daily living. No discomfort at rest.
- Class IV: unable to undertake most activities of daily living without severe discomfort. Discomfort at rest.

Patients with hepatic impairment

VOLIBRIS has not been studied in individuals with severe hepatic impairment (with or without cirrhosis). Since the main routes of metabolism of ambrisentan are glucuronidation and oxidation with subsequent elimination in the bile, hepatic impairment would be expected to increase exposure (C_{max} and AUC) to ambrisentan. Therefore VOLIBRIS should not be initiated in patients with severe hepatic impairment, or clinically significant elevated hepatic aminotransferases (greater than 3 times the Upper Limit of Normal (>3xULN).

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification (2008)

C: Cardiovascular system
C02: Antihypertensives
C02K: Other antihypertensives
C02KX: Other antihypertensives
C02KX02: ambrisentan

2.2. Medicines in the same therapeutic category

Comparator medicines

TRACLEER (bosentan), film-coated tablet, indicated for the treatment of patients with pulmonary arterial hypertension (PAH) classified as WHO functional class III, to improve exercise capacity. Efficacy has been shown in:

- Primary (idiopathic and familial) PAH
- PAH secondary to scleroderma without significant interstitial pulmonary disease

Indications already evaluated by the Committee (see opinion of 5 February 2003)

- PAH associated with congenital systemic-to-pulmonary shunts and Eisenmenger's physiology.

THELIN (sitaxentan), film-coated tablet, indicated for the treatment of patients with pulmonary arterial hypertension (PAH) classified as WHO functional class III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and in pulmonary hypertension associated with connective tissue disease.

2.3. Medicines with a similar therapeutic aim

- REVATIO (sildenafil), phosphodiesterase inhibitor, administered orally
- FLOLAN (epoprostenol sodium), prostacyclin, administered by continuous I.V. infusion
- VENTAVIS (iloprost) 10 µg/ml, solution for inhalation through a nebuliser, prostacyclin analogue
- REMODULIN (treprostinil sodium), prostacyclin analogue administered via continuous subcutaneous infusion.

3 ANALYSIS OF AVAILABLE DATA

The clinical development of ambrisentan (VOLIBRIS) is based on four studies:

- a phase II, randomised double-blind dose-finding study (AMB-220) performed on 64 patients and lasting for 12 weeks, followed by an open-label extension phase
- a phase II hepatic tolerance study (AMB-222) carried out on 36 patients with open-label monitoring
- two phase III randomised double-blind studies versus placebo (studies AMB-320-ARIES 1 and AMB-321 – ARIES 2). These studies underwent open-label monitoring.

This opinion only describes these two comparative studies.

3.1. Efficacy results of the ARIES 1 and ARIES 2 studies

These two studies were conducted with the same objectives and the same methodology.
ARIES 1 assessed VOLIBRIS administered at doses of 5 mg and 10 mg, while ARIES 2 examined VOLIBRIS administered at doses of 2.5 mg and 5 mg.

Objective: to assess the tolerance of ambrisentan and its efficacy in improving exercise capacity in patients with PAH in functional classes II and III compared to that of a placebo on a total of 393 patients suffering from PAH (201 in ARIES 1, 192 in ARIES 2).

Methodology: double-blind, randomised, placebo-controlled phase III studies.
The protocol provided for stratified randomisation according to the aetiology of the PAH (whether or not it was idiopathic)

Inclusion criteria

- age ≥ 18
- idiopathic PAH, PAH associated with forms of collagenosis, administration of anorexigenic substances or HIV infection
- PAH documented by average PAP (pulmonary arterial pressure) ≥25 mmHg, PVR (pulmonary vascular resistance) >3 mmHg/L/min, pulmonary capillary pressure or diastolic left ventricle pressure <15 mmHg
- Distance covered during the 6-minute walk test ≥ 150 m and ≤ 450 m
- WHO functional class I to IV

Exclusion criteria:

- PAH related to congenital or acquired cardiopathy, pulmopathy (interstitial disease or COPD), veno-occlusive disease, post-embolic PAH or sleep apnoea
- prior treatment with a different endothelin receptor antagonist, a phosphodiesterase inhibitor or prostanoids in the four weeks prior to randomisation
- hepatic failure

Administration regimen:
The patients were randomised to receive:

- the placebo
- or ambrisentan at a dose of 5 or 10 mg[2] in the ARIES 1 study
- or ambrisentan at a dose of 2.5 or 5 mg in the ARIES 2 study

N.B.: the results of the ambrisentan 2.5 mg group are presented for information, but readers are reminded that this dose does not have marketing authorisation

[2] Patients randomised in the ambrisentan 10 mg group received the 5 mg dose for the first two weeks of treatment and then the 10 mg dose for the last ten weeks of treatment

Primary efficacy endpoint:
Distance covered during the 6-minute walk test after twelve weeks of treatment[3]

The protocols of both studies specified that 62 patients should be recruited for each treatment group in order to demonstrate a difference of 35 metres between the ambrisentan treatment group and the placebo group with regard to the primary endpoint, with a power of 90% and an alpha error risk of 5% (a method was applied to check inflation of the alpha risk as a result of multiple comparisons).

A pooled analysis of the two doses versus placebo was conducted for each study. This analysis, specified in the protocol, will be presented in this opinion but purely for information, as it was carried out for exploratory purposes.

The pharmaceutical company also submitted a combined analysis of the results of the ARIES 1 and ARIES2 studies, which was not specified in the protocol. This analysis will not be described in this opinion[4].

Secondary endpoints:
- Time to worsening of the patient's clinical condition[5]
- Change in WHO functional class
- Borg dyspnoea index[6]
- Quality of life[7]

Results (ITT population)
The duration of treatment in each study was 12 weeks.

[3] At present there is no recommendation on how the response of patients with PAH to treatment should be assessed. However, assessment must involve evaluating improvement in the patient's NYHA functional class, the distance walked, right ventricular function echographic parameters and/or haemodynamic parameters observed from right cardiac catheterisation (Mc Laughlin V V et al. Pulmonary arterial hypertension. Circulation 2006; 114:1417-31). The distance covered in the 6-minute walk test remains the standard criterion for assessing functional efficacy

[4] According to the EPAR, this analysis, which was not specified in the protocol but was described in the data analysis plan, can be regarded as additional data tending to confirm the data from the individual studies.
However, this analysis must be interpreted with caution; only the results of the two studies taken separately can serve as a basis for conclusions.

[5] From randomisation, the time until one of the following events occurs: death, lung transplant, hospitalisation for PAH, atrial septostomy, termination of the study because of the introduction of a different form of PAH treatment, premature withdrawal from the study

[6] Assessment of dyspnoea on a scale ranging from 0 (no dyspnoea) to 10 (maximum dyspnoea)

[7] SF-36 questionnaire: self-assessment physical functional scale including several items allowing eight physical and mental health indicators to be assessed

Patient characteristics on inclusion (combined results of the two studies)

		ambrisentan				Total
	placebo	2.5 mg	5 mg	10 mg	combined	population
Characteristics	**(n = 132)**	**(n = 64)**	**(n = 130)**	**(n = 67)**	**(n = 261)**	**(n = 393)**
PAH aetiology, n (%)						
Idiopathic PAH	85 (64.4)	42 (65.6)	83 (63.8)	41 (61.2)	166 (63.6)	251 (63.9)
Non-idiopathic PAH	47 (35.6)	22 (34.4)	47 (36.2)	26 (38.8)	95 (36.4)	142 (36.1)
PAH associated with collagenosis	43 (32.6)	19 (29.7)	40 (30.8)	22 (32.8)	81 (31.0)	124 (31.6)
PAH associated with anorexigenic agents	1 (0.8)	1 (1.6)	2 (1.5)	2 (3.0)	5 (1.9)	6 (1.5)
PAH associated with HIV	3 (2.3)	2 (3.1)	4 (3.1)	2 (3.0)	8 (3.1)	11 (2.8)
Time from diagnosis						
Average number of years (SD)	2.2 (3.92)	1.2 (1.93)	2.3 (5.29)	1.4 (2.39)	1.8 (4.05)	2.0 (4.01)
WHO functional class, n (%)						
I	4 (3.0)	0 (0.0)	2 (1.5)	2 (3.0)	4 (1.5)	8 (2.0)
II	47 (35.6)	34 (53.1)	48 (36.9)	22 (32.8)	104 (39.8)	151 (38.4)
III	78 (59.1)	29 (45.3)	73 (56.2)	36 (53.7)	138 (52.9)	216 (55.0)
IV	3 (2.3)	1 (1.6)	7 (5.4)	7 (10.4)	15 (5.7)	18 (4.6)
Average distance covered in the 6-minute walk test (SD)	342.3 (79.55)	347.3 (83.81)	347.2 (80.61)	341.5 (78.28)	345.8 (80.55)	344.6 (80.13)
Average Borg dyspnoea index (SD)	3.8 (2.15)	3.9 (2.43)	3.8 (2.29)	3.8 (2.08)	3.8 (2.26)	3.8 (2.22)

The characteristics of all the patients included were similar.
Most cases of PAH were idiopathic or associated with collagenosis. The majority of the patients included were in functional class II or III.
The median walking distance of patients in functional class II was 380 m [160, 449] in ARIES 1 and 398 m [190, 449] in ARIES 2. For patients in functional class III it was 354 m [192, 442] in ARIES 1 and 350 m [150, 445] in ARIES 2.

> N.B.: according to the French national register of patients with PAH[8], the walking distance for patients in functional class II is 415 ± 86 m and 319 ± 92 m for patients in functional class III.
> The EMEA raised the issue of the representativity of patients included in the study and regarded as falling into functional class II. This was one of the main objections made to the pharmaceutical firm, which was required to supply additional data relating to the characteristics of patients in functional class II to the EMEA in order to confirm the representativity of the patients. The EMEA concluded that the population described in functional class II had less severe disease and needed to be differentiated from patients identified as falling into functional class III.

The concomitant treatments administered were the same for all the treatment groups. A high percentage of patients were pre-treated with calcium inhibitors (between 25% and 50% of patients). Normally, around 20% of patients are treated with calcium inhibitors (after responding to an acute vasoreactivity test)[9].

[8] Humbert M et al. Pulmonary arterial hypertension in France : results from a national registry. Am J Respir Crit Care Med 2006; 173 (9) : 1023-1030

[9] In addition, the proportion of patients treated with calcium inhibitors does not match the number of patients responding to the vasoreactivity test (14.4% of patients in ARIES 1, 23.4% of patients in ARIES 2).

The patients taking part in these two studies had been pre-treated with conventional PAH treatments (digoxin, anticoagulants, diuretics, oxygen or vasodilators: calcium-channel inhibitors and ACE inhibitors).

Results for the primary endpoint:

	ARIES 1 study				**ARIES 2 study**			
	Placebo n = 67	**5 mg group n = 67**	**10 mg group n = 67**	*All doses group n = 134*	**Placebo n = 65**	*2.5mg group n = 64*	**5 mg group n = 63**	*All doses group n = 127*
Average improvement in the walking distance ± standard deviation (m)	**-7.8 (78.88)**	**+22.8 (82.98)**	**+43.6 (65.91)**	*+33.2 (75.37)*	**-10.1 (93.79)**	*+22.2 (82.67)*	**+49.4 (75.36)**	*+35.7 (79.99)*
Average improvement compared to placebo (m)		**+30.6**	**+51.4**	*+41.0*		*+32.3*	**+59.4**	*+45.8*
95%CI p versus placebo		**[2.9;58.3] 0.008**	**[26.6;76.2] <0.001**	*[18.4;63.6] <0.001*		*[1.5;63.1] 0.022*	**[29.6;89.3] <0.001**	*[20.2;71.3] <0.001*

In both studies, after twelve weeks of treatment a statistically significant difference was observed in favour of the ambrisentan treatment groups compared to the placebo group with regard to the criterion of walking distance in the 6-minute test.

Results for this endpoint were presented for patient sub-groups (classified by the aetiology of their PAH, their WHO functional class, etc.). No method of adjusting for multiple comparisons was applied, which means that over-estimation of the effect cannot be ruled out. No formal conclusions can be drawn from these results, which are presented below for information.

In both studies, a statistically significant difference was observed in favour of the ambrisentan treatment groups compared to the placebo group in the sub-group of patients suffering from idiopathic PAH.
For non-idiopathic forms of PAH, a significant difference was observed only in the ARIES 1 study for the 10 mg ambrisentan group.

The following improvements in the walking distance versus placebo were observed among patients in functional class II:

- 25.6 m in the 5 mg ambrisentan group (in ARIES 1, p=0.034)
- 42.0 m in the 10 mg ambrisentan group (in ARIES 1, p=0.004)
- and 67.7 m in the 5 mg ambrisentan group (in ARIES 2, p=0.006)

The following improvements in the walking distance versus placebo were observed among patients in functional class III:

- 56.9 m in the 10 mg ambrisentan group (in ARIES 1, p=0.012)
- and 51.8 m in the 5 mg ambrisentan group (in ARIES 2, p=0.020)

N.B.: the marketing authorisation was granted for patients in functional classes II and III. From a methodological point of view it seems difficult to reach any firm conclusions as to the efficacy of ambrisentan in patients in functional class II.

At the requests of the EMEA an additional analysis was conducted of patients in class II who covered a distance of 415 m or more in the 6-minute walk test on inclusion (this is the average figure noted in the French register). This analysis related to a small number of patients (42 in total). After 12 weeks the improvement in the walking distance was 43.93 m (95% CI [16.04; 71.63], p unknown – result of the combined analysis of both studies).

Results for secondary endpoints:

Study	Group	Secondary endpoints					
		Time to worsening of the patient's clinical condition HR, p value	WHO functional class		Borg dyspnoea index		Quality of life
			% improvement	% worsening	Δ compared to inclusion (SD)	Δ adjusted to placebo, p	
ARIES 1	placebo	NA	23.9%	16.4%	0.0 (2.22)	NA	2.31 ± 7.65
	ambrisentan 5 mg	p : NS	28.4%	1.5%	-0.3 (1.93)	-0.3 p : NS	3.86 ± 7.14 p : NS
			p : NS				
	ambrisentan 10 mg	p : NS	29.9%	4.5%	-0.9 (1.93)	-0.9 p = 0.002	4.52 ± 7.16 p : NS
			p : NS				
	ambrisentan all doses	p : NS	29.1%	3.0%	-0.6 (1.95)	-0.6 p = 0.017	4.10 ± 8.39 p : NS
			p = 0.043				
ARIES 2	placebo	NA	16.9%	18.5%	0.8 (2.63)	NA	-0.20 ± 7.14
	ambrisentan 2.5 mg	80% p = 0.005	15.6%	4.7%	-0.2 (2.17)	-1.0 p = 0.046	3.86 ± 7.14 p = 0.005
			p : NS				
	ambrisentan 5 mg	79% p = 0.008	14.3%	3.2%	-0.4 (1.99)	-1.2 p = 0.040	2.96 ± 6.81 p = 0.040
			p : NS				
	ambrisentan all doses	80% p <0.001	15.0%	3.9%	-0.3 (2.08)	-1.1 p = 0.019	3.41 ± 6.96 p = 0.005
			p : NS				

In the ARIES 1 study, no statistically significant difference between the ambrisentan and placebo treatment groups was observed with regard to the following endpoints:

- time to worsening of the patient's clinical condition
- change in WHO functional class
- quality of life.

A statistically significant difference was observed in favour of the 10 mg ambrisentan group compared to placebo with regard to the 'Borg dyspnoea index' endpoint.

In the ARIES 2 study, a statistically significant difference was observed in favour of each ambrisentan treatment group compared to placebo for all the secondary endpoints except for the 'change in WHO functional class' endpoint.

3.2. Adverse effects in the ARIES 1 and ARIES 2 studies

The safety profile of ambrisentan was assessed on the basis of combined data from both studies (ARIES 1 and ARIES 2).

The adverse events most frequently observed in the ambrisentan groups (n=261) compared to the placebo groups (n=132) were: peripheral oedema (17.2% versus 10.6%), headache (14.6% versus 13.6%), vertiginous sensations (6.9% versus 9.8%) and nasal congestion (5.7% versus 1.5%).

Peripheral oedema was reported more frequently in the 10 mg ambrisentan group (28.4% of patients) than in the 5 mg group (18.5%) and the placebo group (10.6%). The incidence of oedema was higher among patients in functional class III than those in functional class II both in the placebo group (12.8% versus 6.4%) and in all the ambrisentan groups (21.7% versus 10.6%).

A fall in haemoglobin levels of ≥ 1 g/dL was seen in 65.5% of patients (171/231) treated with ambrisentan versus 17.4% of patients (23/132) in the placebo groups.

No transaminase elevation to over three times the ULN (upper limit of the norm) was observed in patients being treated with ambrisentan (elevated transaminase levels were noted in 2.3% of patients receiving the placebo).
Ten patients in the ambrisentan group stopped treatment as a result of adverse events.

3.3. Conclusion

The tolerance of ambrisentan and its efficacy in improving exercise capacity in patients with PAH in functional classes II and III have been assessed in two studies carried out on a total of 393 patients suffering from PAH (201 in ARIES 1, 192 in ARIES 2). These two phase III, double-blind, randomised studies versus placebo investigated three doses of ambrisentan. The duration of treatment in each study was 12 weeks. This is not long enough to assess long-term efficacy and improvement in survival[10].
Most cases of PAH were idiopathic or associated with collagenosis. The majority of the patients included were in functional class II or III. A pooled analysis of ambrisentan doses was performed. This analysis, specified in the protocol, was exploratory in nature.

In each study, after 12 weeks of treatment a statistically significant difference was observed in favour of each ambrisentan treatment group compared to the placebo group with regard to the primary endpoint (distance covered in the 6-minute walk test). However, the improvements were modest, ranging from 30.6 metres to 59.4 metres.

Results for this endpoint were presented for patient sub-groups (classified by the aetiology of their PAH, their WHO functional class, etc.). These analyses, which were specified in the protocol but were of an exploratory nature, cannot be taken into consideration.

In the ARIES 1 study, no statistically significant difference between the two ambrisentan treatment groups and the placebo group was observed with regard to the secondary endpoints (time to worsening of the patient's clinical condition, change in the WHO functional class, quality of life), except in the 10 mg ambrisentan group with regard to the 'Borg dyspnoea index' endpoint.
In the ARIES 2 study, a statistically significant difference was observed between each ambrisentan treatment group compared to placebo for all the secondary endpoints except for the 'change in WHO functional class' endpoint.

No long-term comparative data and no data versus an active comparator is available. A study versus TRACLEER would have been possible given the development dates of each of the proprietary products.
It would have been useful to have an assessment of a haemodynamic criterion, such as pulmonary vascular resistance levels, in a comparative study to back up the clinical data.
Furthermore, efficacy has not been clearly demonstrated among patients in functional class II.

The main adverse events observed among patients taking ambrisentan compared to those taking placebo were peripheral oedema, headache, nasal congestion and a decline of ≥ 1 g/dL in haemoglobin levels. The studies did not find ambrisentan to be hepatotoxic.
The tolerance profile was found to be similar to that observed for other endothelin inhibitors, except for hepatotoxicity.

[10] EPAR ambrisentan p.23

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

PAH is a potentially fatal disease characterised by an increase in blood pressure in the pulmonary arterial system. The most common clinical signs are asthenia, dyspnoea, chest pain and loss of consciousness. The life expectancy of patients receiving symptomatic treatment is short (around 2.8 years).
These proprietary drugs are intended to provide symptomatic treatment.
The efficacy/safety ratio is high.
It is used for first-line therapy.
There are alternative drug therapies.

Public health benefit:
Pulmonary arterial hypertension (PAH), whether idiopathic or associated with collagenosis and whether the patient falls into functional class II or III, is a minor public health burden in view of the small number of patients affected.
Improving the management of pulmonary arterial hypertension, whether idiopathic or associated with collagenosis, is a public health need as part of an established priority (Rare diseases plan).
In the light of the results of trials, and in view of existing treatments, the proprietary product VOLIBRIS is not expected to have any impact in population terms on morbi-mortality and quality of life associated with PAH.
The information available does not indicate that the proprietary product VOLIBRIS will make an additional contribution to the identified need.
Consequently, in the current state of knowledge, VOLIBRIS is not expected to offer any public health benefit in this indication.

The actual benefit is substantial, until the Transparency Committee conducts a reassessment of all the treatments for PAH.

4.2. Improvement in actual benefit

As no comparative studies are available, the Committee has been unable to quantify the contribution made by VOLIBRIS compared to existing treatments. The Transparency Committee therefore considers that VOLIBRIS offers no improvement in actual benefit (IAB V) compared to the proprietary products available that are indicated in the treatment of idiopathic pulmonary arterial hypertension and PAH associated with systemic collagenosis.

4.3. Therapeutic use [11]

The conventional approach to treating PAH consists of limiting physical activity and administering anticoagulants, diuretics, oxygen therapy and calcium inhibitors.
The development of new orally administered pulmonary vasodilators has altered the therapeutic approach, especially for patients in NYHA class III. It now seems rational to start these patients on an effective, simple and well-tolerated treatment: bosentan (TRACLEER) or sildenafil (REVATIO), both of which are administered orally. Sitaxentan (THELIN), which is also administered orally, is an additional treatment option for managing primary PAH and PAH associated with collagenosis.

11 ESC guidelines on the diagnosis and treatment of pulmonary arterial hypertension. Eur Heart J 2004; 25:2243-78. Deanfield J et al. Management of grown up congenital heart disease. Task force on the management of grown up congenital heart disease. European Society of Cardiology. Eur Heart J 2003;24:1035-84.

Iloprost (VENTAVIS), an inhalational prostacyclin, can be regarded as an alternative to bosentan, but the limitations associated with the mode of administration must be kept in mind. In particular, it can be administered to patients for whom bosentan is contraindicated or who show hepatic intolerance to bosentan.
In 2004 the European Society of Cardiology issued guidelines indicating that treprostinil (REMODULIN) administered by continuous subcutaneous infusion could be offered to patients suffering from class III PAH on the same basis as iloprost (VENTAVIS). Practitioners considering starting a patient on treprostinil (REMODULIN) must bear in mind that the patient is very likely to need to continue receiving the drug via subcutaneous infusion for a prolonged period, in the context of long-term treatment. When a patient needs to be transferred to intravenous epoprostenol treatment (FLOLAN), close medical supervision is required during the transition period.
The prognosis of most patients in NYHA functional class IV has been markedly improved by the availability of a prostacyclin that can be administered by continuous intravenous infusion (epoprostenol (FLOLAN)). However, this treatment is inconvenient and can lead to risks of infection associated with the administration system (indwelling central catheter).
Pulmonary or cardiopulmonary transplant are interventions of last recourse. These procedures are usually considered for patients who are on drug treatment and whose condition has not improved after three months.

Ambrisentan (VOLIBRIS) is an additional therapeutic option in the management of primary PAH and PAH associated with systemic collagenosis in patients in functional class III. Its role is difficult to establish in the absence of comparative data versus other treatments for PAH, in particular TRACLEER.
VOLIBRIS is currently the only treatment for PAH that is indicated for patients in functional class II. Its role in treating these patients remains to be defined, given the absence of other validated treatments for this indication and the absence of recommendations.

4.4. Target population

The target population of VOLIBRIS corresponds to adult patients:
- suffering from primary PAH
- suffering from PAH associated with connective tissue disease
- in functional class II and III (NYHA classification).

The target population can be estimated on the basis of the following data:
- Idiopathic PAH is a rare disease that affects between 600 and 700 people in France.
- Among them, approximately 20% of them will be in NYHA Class II, 60% in Class III.
- PAH associated with connective tissue disease mainly relates to systemic scleroderma, systemic lupus erythematosus, dermatomyositis, mixed connective tissue disease and in some cases, rheumatoid arthritis.
- The available data do not enable the target population to be estimated, except with a major degree of uncertainty.
- Of the 9,500 patients in France suffering from systemic scleroderma (expert's opinion), around 12% will have PAH, i.e. approximately 1,150 patients.
- Of the 50,000 patients suffering from systemic lupus erythematosus (expert's opinion), around 2.8% will have PAH, i.e. 1,400 patients.
- Of the 2,000 patients suffering from mixed connective tissue disease (expert's opinion), around 15% will have PAH, i.e. 300 patients.
- Of these patients, around 60% will be in functional class III.

On this basis, the target population of VOLIBRIS is approximately 3,000 patients.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services for the indication and at the dosage in the marketing authorisation.