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TRANSPARENCY COMMITTEE

OPINION

5 January 2011

List of proprietary products concerned:

ENDOTHELIN ANTAGONISTS
- TRACLEER 62.5 mg, 125 mg film-coated tablets – 32 mg, dispersible tablets, bosentan
- THELIN 100 mg, coated tablets, sitaxentan
- VOLIBRIS 5 mg and 10 mg film-coated tablets, ambrisentan

PHOSPHODIESTERASE INHIBITORS
- REVATIO 20 mg, film-coated tablets, sildenafil
- ADCIRCA 20 mg, film-coated tablets, tadalafil

PROSTACYCLINS
- REMODULIN 1 mg/ml, 2.5 mg/ml, 5 mg/ml, 10 mg/ml solution for infusion (subcutaneous route), treprostinil sodium
- FLOLAN 0.5 mg, 1.5 mg, powder and solvent for solution for injection, epoprostenol sodium
- VENTAVIS 10 micrograms/ml, nebuliser solution, iloprost

Reason for the review: Reassessment of the Actual Benefit and Improvement in Actual Benefit in accordance with article R-163-21 of the Social Security Code.

Medical, Economic and Public Health Assessment Division

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BACKGROUND AND INTRODUCTION

The transparency Committee (TC) of HAS assesses medicinal products that have obtained a marketing authorisation when the company marketing them wishes them to be entered into the list of medicines refundable by National Health Insurance (articles L.162-17 of the Social Security Code and L.5123-2 of the Public Health Code) or on request.

The TC is a scientific body comprised of medical practitioners, pharmacists and specialists in methodology and epidemiology. Its objectives are:

- to provide an opinion to the ministers responsible for health and social security concerning the validity of the management of medicinal products by social security and/or of their use in hospital, notably with respect to their actual benefit (AB) as well as the improvement in actual benefit (IAB) they are likely to provide in comparison with the treatments that are already available;
- to contribute to the proper use of medicinal products by publishing relevant, independent scientific information concerning the products.

These objectives are defined in the Social Security Code, in particular in articles R.163-2 to R.163-21, L.161-37, L.161-39 and L.161-41.
According to articles L. 162-17, L. 161-37, L.161-39, L. 161-41, L. 161-44, R. 163-2 to R. 163-21, R. 161-71, R. 161-76, R. 161-85 of the Social Security Code and articles L. 5123-2 and L. 5123-3 of the Public Health Code, the TC's opinion specifies the actual benefit and improvement in actual benefit provided by the medicinal product. This assessment is performed on the basis of a critical analysis of the scientific literature, on the basis of *Evidence Based Medicine* and the opinion of experts, with respect to the indications and dosages cited in the marketing authorisation.

I. Objective of the transparency Committee initiative

In accordance with article R-163-21 of the Social Security Code, the transparency Committee is acting on its own initiative to provide an opinion of the efficacy and tolerance of these medicinal products, in the light of the new proprietary products that have been developed for the treatment of pulmonary arterial hypertension (PAH), recent data from the literature and the dossiers submitted by the manufacturers concerned.

II. General description

The list of proprietary products included in the assessment is presented in Table 1. The indications, results of studies available during the inclusion process and the levels of AB and IAB assigned by the transparency Committee have been specified there (see Table 2 in Appendix 1 for the dosages and principal warnings and precautions for use).

II.1 Endothelin antagonists

TRACLEER 62.5 mg, film-coated tablet
B/56 (CIP code: 563 621-1)
TRACLEER 125 mg, film-coated tablet
B/56 (CIP code: 563 622-8)
TRACLEER 32 mg, dispersible tablets
B/56 (CIP code: 399 351-0)

Applicant: ACTELION PHARMACEUTICALS FRANCE
bosentan
Date of European Marketing Authorisation (centralised): 15 May 2002
List I
Medicine for hospital prescription only.
Prescription restricted to specialists and/or hospital departments specialising in respiratory medicine, cardiology, rheumatology, dermatology, or internal medicine.
Medicine requiring special monitoring during treatment.
Orphan medicinal product (initial date of designation for TRACLEER proprietary products: 14 February 2001)

THELIN 100 mg, coated tablets
B/28 (CIP code: 379 171-7)

Applicant: PFIZER
sitaxentan
Date of Marketing Authorisation (centralised procedure): 10 August 2006
Orphan medicinal product (date of designation: 21 October 2004)
List I
Medicine for hospital prescription only, with prescription restricted to specialists and/or hospital departments specialising in cardiology, respiratory medicine or internal medicine.
Medicine requiring special monitoring during treatment.

VOLIBRIS 5 mg, film-coated tablets
B/30 (CIP code: 386 578-1)
VOLIBRIS 10 mg, film-coated tablets
B/30 (CIP code: 386 580-6)

Applicant: GSK (GlaxoSmithKline)
ambrisentan
Date of Marketing Authorisation (centralised procedure): 21 April 2008
Orphan medicinal product (date of designation: 11 April 2005)
List I
Medicine for hospital prescription only, with prescription restricted to specialists and/or hospital departments specialising in respiratory medicine, cardiology or internal medicine.
Medicine requiring special monitoring during treatment.

ATC Code (2010):
C: Cardiovascular system
C02: Antihypertensives
C02K: Other antihypertensives
C02KX: Other antihypertensives
C02KX01: bosentan
C02KX02: ambrisentan
C02KX03: sitaxentan

II.2 Phosphodiesterase inhibitors

REVATIO 20 mg, film-coated tablets
B/90 (CIP code: 370 240-6)

Applicant: PFIZER
sildenafil
Date of Marketing Authorisation (centralised procedure): 28 October 2005
Orphan medicinal product (date of designation: 12 December 2003 for sildenafil in the treatment of PAH).
List I
Medicine for hospital prescription only, with prescription restricted to specialists and/or hospital departments specialising in respiratory medicine, cardiology or internal medicine.

ADCIRCA 20 mg, film-coated tablets
B/28 (CIP code: 347 152-7)
B/56 (CIP code: 347 153-3)

Applicant: LILLY FRANCE
tadalafil
Date of Marketing Authorisation (centralised procedure): 30 November 2009
List I
Medicine for hospital prescription only, restricted to specialists and/or departments specialising in pneumology, cardiology or internal medicine.

ATC Code (2010):
G: Genitourinary system and sex hormones
G04: Urologicals
G04B: Other urologicals, including antispasmodics
G04BE: Drugs used in erectile dysfunction
G04BE03: sildenafil
G04BE08: tadalafil

II.3 Prostacyclins

FLOLAN 0.5 mg, powder and solvent for solution for injection
1 vial of 50 ml (CI code: 561 400-8)
FLOLAN 1.5 mg, powder and solvent for solution for injection
1 vial of 50 ml (CIP code: 561 398-3)

Applicant: GSK (GlaxoSmithKline)
epoprostenol sodium
Date of Marketing Authorisation (national procedure): 06 March 1998
List I
Medicine for hospital prescription only, with prescription restricted to specialists and/or hospital departments specialising in respiratory medicine or cardiology.

VENTAVIS 10 micrograms/ml, nebuliser solution
B/ 30 ampoules each of 1 ml (CIP: 375 480-5)
B/30 ampoules each of 2 ml (CIP: 564 920-2)

Applicant: BAYER SANTE
iloprost

Date of Marketing Authorisation for 2 ml ampoules (centralised procedure): 16 September 2003
Date of Marketing Authorisation for 1 ml ampoules (centralised procedure): 02 May 2006
Marketing authorisation granted under exceptional circumstances.
The results of an observational study, which was requested by the CHMP (Committee for Human Medicinal Products) and which aims to collect data on long-term efficacy and tolerance, are expected in the 4th quarter of 2012.
Orphan medicinal product (date of designation: 29 December 2000)
List I
Medicine for hospital prescription only, with prescription restricted to specialists and/or hospital departments specialising in respiratory medicine or cardiology.

REMODULIN 1 mg/ml, solution for infusion (subcutaneous route)
1 glass vial of 20 ml (CIP code: 368 161-5)
REMODULIN 2.5 mg/ml, solution for infusion (subcutaneous route)
1 glass vial of 20 ml (CIP code: 368 162-1)
REMODULIN 5 mg/ml, solution for infusion (subcutaneous route)
1 glass vial of 20 ml (CIP code: 368 163-8)
REMODULIN 10 mg/ml, solution for infusion (subcutaneous route)
1 glass vial of 20 ml (CIP code: 368 164-4)

Applicant: BIOPROJET PHARMA
treprostinil sodium
Date of Marketing Authorisation (mutual recognition procedure): 28 February 2005
List I
Medicine for hospital prescription only, with prescription restricted to specialists and/or hospital departments specialising in respiratory medicine or cardiology.

ATC Code (2010):
B : Blood and blood-forming organs
B01 : Antithrombotic agents
B01A : Antithrombotic agents
B01AC : Inhibitors of platelet aggregation, excluding heparin
B01AC09: epoprostenol
B01AC11: iloprost
B01AC21: treprostinil

Table 1:

Proprietary product	INN Route of administration	Indication in marketing authorisation (Date of marketing authorisation)	Results of studies supplied to the Committee concerning the primary efficacy endpoint: distance walked in 6 minutes	Conclusions of the Committee (AB, IAB, Date of the opinion)
Medicinal products in the same therapeutic category				
Endothelin antagonists:				
TRACLEER 62.5 mg and 125 mg	Bosentan Oral route	Treatment of PAH to improve exercise capacity and symptoms in patients in functional class III. Efficacy was demonstrated in primary PAH and in PAH secondary to scleroderma without significant associated interstitial disease. (date of marketing authorisation: 15 May 2002) Included on the list of medicines approved for hospital use since 19 March 2003	- in a study in 32 subjects with stage III primary PAH (and 4 subjects with PAH secondary to scleroderma), a significant improvement was observed in the distance walked in 6 minutes: gain around 51 m for patients treated with bosentan 125 mg x2/day after 12 weeks of treatment compared to those receiving placebo. - in the BREATHE-1 study in 213 subjects, of whom 150 had primary PAH and 47 PAH secondary to scleroderma, a significant improvement was observed in the distance walked in 6 minutes: gain of the order of 44 m for patients treated with bosentan after 16 weeks of treatment compared to those receiving placebo.	Opinion of the TC of 5 February 2003: Substantial AB TRACLEER has the same IAB as FLOLAN (IAB I) in patients with primary PAH or PAH secondary to scleroderma. Its administration by the oral route is a significant advantage
TRACLEER 62.5 mg and 125 mg	Bosentan Oral route	Treatment of pulmonary arterial hypertension associated with left-to-right shunt congenital heart disease with Eisenmenger syndrome. (date of marketing authorisation: 27 October 2006)	The efficacy and tolerance of TRACLEER were evaluated in patients with functional class III pulmonary arterial hypertension associated with left-to-right shunt congenital heart disease with Eisenmenger syndrome in a comparative, placebo-controlled, randomised, double-blind study in 54 patients (37 in the TRACLEER group, 17 in the placebo group). In this study, it was planned to analyse 2 endpoints: a comparison between TRACLEER and placebo of the change in transcutaneous oxygen saturation determined between the start and end of treatment according to a hypothesis of non-inferiority; a comparison between TRACLEER and placebo of the change in pulmonary vascular resistance determined between the start and end of treatment according to a hypothesis of superiority. The non-inferiority of TRACLEER with respect to placebo having been previously demonstrated for the criterion "change in transcutaneous oxygen saturation", a statistically significant decrease in pulmonary	Opinion of the TC of 18 July 2007: Substantial AB TRACLEER provides a moderate improvement in actual benefit (IAB III) in the management of pulmonary arterial hypertension associated with left-to-right shunt congenital heart disease with Eisenmenger syndrome.

Proprietary product	INN Route of administration	Indication in marketing authorisation (Date of marketing authorisation)	Results of studies supplied to the Committee concerning the primary efficacy endpoint: distance walked in 6 minutes	Conclusions of the Committee (AB, IAB, Date of the opinion)
			vascular resistance was observed for TRACLEER and placebo between the start and the end of treatment (decrease of 472.01 dyne.sec.cm^{-5}). However, this decrease was moderate and related to an intermediate endpoint.	
TRACLEER 62.5 mg and 125 mg	Bosentan Oral route	Some improvements were also demonstrated in patients with pulmonary arterial hypertension (PAH) in the WHO II functional class (date of extension of indication: 29 July 2008) Included on the list of medicines approved for hospital use since 21 October 2008	The efficacy and tolerance of bosentan in patients with PAH in functional class II were evaluated in the EARLY phase III, placebo-controlled, randomised, double-blind study conducted in 185 patients with PAH. After 6 months of treatment, the difference of 19.1m observed in comparison to placebo with respect to the criterion "distance covered in the 6-minute walking test" was not statistically significant. Furthermore, this difference was lower than the threshold of 35 m considered to be clinically relevant.	Opinion of the TC of 21 January 2009: The actual benefit is considered to be substantial, pending reassessment of all therapies for PAH by the transparency Committee. IAB: On the basis of the available clinical data, the Committee was not able to quantify the contribution of TRACLEER in the management of patients with pulmonary arterial hypertension in functional class II. The transparency Committee therefore considers that TRACLEER does not provide an improvement in actual benefit (IAB V) in the management of idiopathic pulmonary arterial hypertension or pulmonary arterial hypertension associated with connective tissue disease or congenital heart disease in patients in functional class II.
TRACLEER 32 mg	Bosentan Oral route	Treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients in WHO functional class III[1]. Efficacy has been shown in: - primary (idiopathic and familial) pulmonary arterial hypertension; - pulmonary arterial hypertension	The FUTURE-1 pharmacokinetics study specifically evaluated TRACLEER 32 mg in 36 children aged from 2 to 12 years with idiopathic or familial PAH of functional class II or III. There are no efficacy studies available, which have been conducted specifically in children, particularly those with PAH associated with	Opinion of the TC of 10 February 2010: The actual benefit is considered to be substantial, pending reassessment of all therapies for PAH by the transparency Committee.

[1] Barst RJ et al. Diagnosis and differential assessment of pulmonary arterial hypertension. J Am Coll Cardiol 2004; 43: S40-S47. The NYHA classification (New York Heart Association Functional Classification) is based on the functional capacity of the patient. It divides patients into 4 classes:

- Class I : no limitation of physical activities. No dyspnoea and no fatigue during everyday activities
- Class II : moderate limitation of physical activities. Discomfort during strenuous physical activities. No discomfort at rest.
- Class III : marked limitation of physical activities. Discomfort during even moderate everyday activities. No discomfort at rest.
- Class IV : unable to undertake most everyday activities without considerable discomfort. Discomfort at rest.

Proprietary product	INN Route of administration	Indication in marketing authorisation (Date of marketing authorisation)	Results of studies supplied to the Committee concerning the primary efficacy endpoint: distance walked in 6 minutes	Conclusions of the Committee (AB, IAB, Date of the opinion)
		secondary to scleroderma without significant associated interstitial disease; - pulmonary arterial hypertension associated with left-to-right shunt congenital heart disease with Eisenmenger syndrome. Some improvements have also been shown in patients with pulmonary arterial hypertension (PAH) in WHO functional class II. TRACLEER is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and progressive digital ulcer disease (Date of marketing authorisation: 1st July 2009). Included on the list of medicines approved for hospital use since 18 June 2010	congenital heart disease, a very common aetiology in children.	IAB: In the absence of clinically relevant data, the transparency Committee is unable to quantify the contribution of TRACLEER 32 mg dispersible tablets in the management of patients with primary PAH or PAH associated with scleroderma or congenital heart disease in functional class II or III . It is a useful addition to the therapeutic battery for the management of PAH, particularly in children. TRACLEER 32 mg dispersible tablets do not provide an improvement in actual benefit (IAB V).
THELIN	Sitaxentan Oral route	Treatment of pulmonary arterial hypertension with the aim of improving the exercise capacity of patients in functional class III (WHO classification). The efficacy of the treatment was demonstrated for primary pulmonary arterial hypertension and pulmonary arterial hypertension associated with connective tissue disease. (date of marketing authorisation: 10 August 2006) Included on the list of medicines approved for hospital use since 10 August 2007	- study FPH02: comparative, randomised, double-blind study in 247 patients with PAH. An improvement of 31.4 metres, which was statistically significant was observed in the 6-minute walking test (primary study endpoint, 95% CI [5.4; 57.4], p = 0.03). - study FPH04: phase III, comparative, randomised, double-blind study in 98 patients with PAH. The improvement in the walking distance with THELIN compared to placebo was 24.3 m. This difference was not statistically significant.	Opinion of the TC of 20 June 2007: Substantial AB The Committee was not able to quantify the contribution of THELIN compared to existing treatments due to the absence of comparative studies with methodology of a good quality. The transparency Committee is therefore of the opinion that THELIN does not offer an improvement in actual benefit (IAB V) compared to the available proprietary products that are indicated in the treatment of primary pulmonary arterial hypertension and pulmonary arterial hypertension associated with connective tissue disease
VOLIBRIS	Ambrisentan Oral route	VOLIBRIS is indicated in the treatment of pulmonary arterial hypertension (PAH) in patients in functional classes II and III (WHO classification) in order to improve exercise capacity. Its efficacy has been demonstrated in idiopathic PAH and in PAH associated with systemic collagen tissue	The tolerance of ambrisentan and its efficacy with respect to exercise capacity in PAH patients in functional classes II and III were evaluated in two phase III, placebo-controlled, randomised double-blind comparative studies, 12 weeks in duration, which included a total of 393 patients with	Opinion of the TC of 16 July 2008: The actual benefit is considered to be substantial, pending reassessment of all therapies for PAH by the transparency Committee.

Proprietary product	INN Route of administration	Indication in marketing authorisation (Date of marketing authorisation)	Results of studies supplied to the Committee concerning the primary efficacy endpoint: distance walked in 6 minutes	Conclusions of the Committee (AB, IAB, Date of the opinion)
		disease. (date of marketing authorisation: 21 April 2008) Included on the list of medicines approved for hospital use since 21 October 2008	primarily idiopathic PAH or PAH associated with connective tissue disease. In each study, after 12 weeks of treatment, a statistically significant difference was observed in favour of the ambrisentan treatment groups compared to the placebo group with respect to the primary efficacy endpoint of distance walked in the 6-minute walking test (improvement of 30.6 m in the 5 mg group and 51.4 m in the 10 mg group in the ARIES 1 study, and improvement of 59.4 m in the ARIES 2 study)	The Committee was not able to quantify the contribution of VOLIBRIS compared to existing treatments due to the absence of comparative studies. The transparency Committee is therefore of the opinion that VOLIBRIS does not offer an improvement in actual benefit (IAB V) compared to the available proprietary products that are indicated in the treatment of idiopathic pulmonary arterial hypertension and pulmonary arterial hypertension associated with systemic collagen disease
Medicines with a similar therapeutic aim				
Phosphodiesterase inhibitor:				
REVATIO	Sildenafil Oral route	Treatment of PAH in patients in functional class III according to the WHO classification, in order to improve exercise capacity. Its efficacy has been demonstrated in idiopathic PAH and in PAH associated with connective tissue disease. (date of marketing authorisation: 28 October 2005) Included on the list of medicines approved for hospital use since 12 April 2006	Phase III, placebo-controlled, randomised, double-blind study conducted in 277 subjects. After 12 weeks of treatment, the mean increase in walking distance over 6 minutes, compared to baseline and corrected with respect to placebo, was 45 metres ($p < 0.0001$).	Opinion of the TC of 15 February 2006: Substantial AB REVATIO offers the same IAB as TRACLEER[1]
ADCIRCA	Tadalafil Oral route	ADCIRCA is indicated in adults for the treatment of pulmonary arterial hypertension (PAH) classified as WHO functional class II and III[2], to improve exercise capacity. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH related to collagen vascular disease. (date of marketing authorisation: 30 November 2009)	The efficacy and tolerance of tadalafil (ADCIRCA) in patients with PAH in functional classes II and III was evaluated in the LVGY placebo-controlled, randomised, double-blind, phase III study, which included 406 patients with PAH (82 in the placebo group, 79 in the group receiving tadalafil 40 mg, the recommended dosage in the Marketing Authorisation). After 16 weeks of treatment, the difference of 26.0	Opinion of the TC of 21 July 2010: The actual benefit is classed as moderate, pending reassessment of PAH therapies. IAB: The Committee was not able to quantify the contribution of the proprietary product ADCIRCA compared to existing treatments due to the absence of comparative

[2] The NYHA classification (New York Heart Association Functional Classification) is based on the functional capacity of the patient. It divides patients into 4 classes:
- Class I : no limitation of physical activities. No dyspnoea and no fatigue during everyday activities
- **Class II : moderate limitation of physical activities. Discomfort during strenuous physical activities. No discomfort at rest.**
- **Class III : marked limitation of physical activities. Discomfort during even moderate everyday activities. No discomfort at rest.**
- Class IV : unable to undertake most everyday activities without considerable discomfort. Discomfort at rest.

Proprietary product	INN Route of administration	Indication in marketing authorisation (Date of marketing authorisation)	Results of studies supplied to the Committee concerning the primary efficacy endpoint: distance walked in 6 minutes	Conclusions of the Committee (AB, IAB, Date of the opinion)
		Included on the list of medicines approved for hospital use since 10 September 2010	m [9.5; 44.0] observed in comparison to placebo with respect to the criterion "distance covered in the 6-minute walking test" was statistically significant.	studies. The transparency Committee is therefore of the opinion that ADCIRCA does not offer an improvement in actual benefit (IAB V) compared to the available proprietary products that are indicated in the treatment of idiopathic pulmonary arterial hypertension and pulmonary arterial hypertension associated with connective tissue disease.
Prostacyclins:				
FLOLAN	Epoprostenol IV infusion (central catheter)	Long-term treatment, by continuous infusion, of severe primary pulmonary arterial hypertension (PPAH), when the following conditions are met: - A diagnosis of secondary pulmonary arterial hypertension will have already been eliminated, - The PAH is at clinical stage III or IV (on the severity scale of the New York Heart Association), - At least one of the haemodynamic criteria of seriousness is present: - pulmonary vascular resistance (PVR) greater than 20 IU/m^2, - cardiac index (CI) below 2.5 l/min/m^2, Right atrial pressure (RAP) greater than 10 mmHg, - venous oxygen saturation (SVO2) less than 63%, - treatment with oral vasodilator is ineffective (for information, a reversibility test with nitric oxide can be performed in order to identify potential responders to oral vasodilator treatment).	During chronic administration, treatment with epoprostenol has been proven to have a beneficial, dose-dependent effect on haemodynamic parameters, with an improvement in cardiac function as well as pulmonary vasodilation. FLOLAN enables a significant prolongation of the survival of patients with primary PAH stages III and IV, thus enabling them to wait for a potential transplant. FLOLAN also enables improvement in functional disability (walking time) and quality of life.	<u>Opinion of the TC of 27 May 1998:</u> Inclusion on the list for hospital use Substantial AB FLOLAN provides a major IAB (level I) in terms of improved survival and quality of life. This is the first medicinal product indicated in PAH stages III and IV.
		FLOLAN is indicated for long-term treatment, by means of continuous infusion, of pulmonary arterial hypertension (PAH): - idiopathic, familial or sporadic pulmonary arterial hypertension, - pulmonary arterial hypertension associated with systemic collagen disease. In patients in functional clinical stage III or IV (on	A randomised, multicentre study, which included 111 patients with moderate to severe PAH associated with scleroderma, compared the efficacy of epoprostenol given by continuous infusion and combined with conventional treatments (n=56) with conventional treatments alone (n=55) over a period of 12 weeks. After 12 weeks of treatment, the distance walked	<u>Opinion of the TC of 8 June 2005:</u> inclusion on the list of medicines in the extension of indication: PAH associated with systemic collagen disease. Substantial AB FLOLAN provides a level II IAB.

Proprietary product	INN Route of administration	Indication in marketing authorisation (Date of marketing authorisation)	Results of studies supplied to the Committee concerning the primary efficacy endpoint: distance walked in 6 minutes	Conclusions of the Committee (AB, IAB, Date of the opinion)
		the severity scale of the New York Heart Association). (date of marketing authorisation: 6 March 1998, corrected on 13 December 2004) Included on the list of medicines approved for hospital use since 19 July 1998	in 6 minutes had increased (from 270 m to 316 m) in the epoprostenol group, while it had decreased (from 240 m to 192 m) in the group given conventional treatments. The difference between the two groups was 108 metres [95% CI: 55.2 to 180, p< 0.01]	
VENTAVIS	Iloprost Inhalation (nebulisation)	Treatment of primary PAH to improve exercise capacity and symptoms in patients in functional class III. (date of marketing authorisation: 16 September 2003) Included on the list of medicines approved for hospital use since: 1 ml: 6 July 2007 2 ml: 4 June 2004	In the principal study (placebo-controlled phase III study), iloprost administered by inhalation improved exercise capacity and symptoms in 203 patients with PAH in functional class III. In addition, after 12 weeks of treatment, the result of the 6-minute walking test was increased by a mean of 22 metres in the iloprost group while decreasing by a mean of -3.3 metres in the placebo group.	Opinion of the TC of 7 April 2004: Substantial AB According to the therapeutic strategy, the population likely to benefit most from VENTAVIS comprises patients with contraindications or hepatic intolerance to TRACLEER, for whom administration of FLOLAN is not appropriate. In this population, VENTAVIS provides IAB II. For other patients with this therapeutic indication, VENTAVIS does not provide IAB with respect to TRACLEER
REMODULIN	Treprostinil Continuous subcutaneous infusion	Treatment of primary pulmonary arterial hypertension to improve exercise capacity and symptoms of the disease in patients in NYHA (New York Heart Association) functional class III. (date of marketing authorisation: 28 February 2005) Included on the list of medicines approved for hospital use since 28 October 2005	Two placebo-controlled, randomised, double-blind phase III clinical studies were conducted with REMODULIN (treprostinil) in 469 subjects with stable PAH. After 12 weeks of treatment, the mean change in the 6-minute walking test, compared to baseline value, was -2 ± 6.61 metres in the treprostinil group and -21.8 ± 6.18 metres in the placebo group, with a relative difference between the treprostinil and placebo groups of 19.7 metres (p=0.0064).	Opinion of the TC of 20 July 2005: Substantial AB REMODULIN offers the same IAB as VENTAVIS

II.4 Supplementary data: Results of studies already evaluated by the TC concerning the principal secondary endpoints: change in WHO functional class and interval to clinical exacerbation[3].

It should be noted that these results, being secondary endpoints of the studies, are presented for the purposes of information.

Endothelin antagonists:
- with TRACLEER, after 12 weeks of treatment the functional class was improved and no clinical deterioration was observed in the bosentan arm, while 3 patients in the placebo arm had to receive epoprostenol (study 351). In the EARLY study, a statistically significant difference was observed in favour of the bosentan group over placebo with respect to:
  - the interval to clinical exacerbation (primarily due to progression of PAH symptoms)[4]
  - deterioration in functional class: 3 patients on bosentan deteriorated in functional class III or IV versus 12 patients on placebo.

- with VOLIBRIS, in one of the studies (ARIES 2), a statistically significant difference was observed in favour of each ambrisentan treatment group over placebo with respect to the secondary endpoints: interval to clinical exacerbation and quality of life.

Phosphodiesterase inhibitors:
- with REVATIO, at the end of 12 weeks of treatment there was improvement of at least one functional class in 28% of patients treated with REVATIO 20 mg 3 times/day (n=69) and 7% of patients on placebo (n=70). No difference was observed between the groups with respect to the criterion "interval to clinical exacerbation".
- with ADCIRCA, no difference was observed between the tadalafil treatment group and the placebo group with respect to the criterion "change in functional class". A clinical exacerbation was observed in 13 patients in the placebo group and 4 in the tadalafil group.

Prostacyclins:
- with FLOLAN, an improvement in functional class was observed in 21/56 patients in the epoprostenol group but in none of the patients in the control group (treated with conventional treatments)
- VENTAVIS, there was an improvement in functional class in 26% of patients in the iloprost group (n=101) and 15% of patients in the placebo group (n=102)
- with respect to REMODULIN, no information is available concerning these endpoints.

[3] Interval following randomisation until the occurrence of one of the following events: death, lung transplantation, admission to hospital due to exacerbation of PAH, atrial septostomy, introduction of another treatment for PAH, deterioration in WHO functional class

[4] Clinical exacerbation was noted in 13/92 patients in the placebo group (9 patients had progression of symptoms associated with PAH, 3 were admitted to hospital for PAH-related complications, 1 patient died) and 3/93 patients in the bosentan group (1 patient had progression of symptoms associated with PAH, 1 was admitted to hospital for PAH-related complications, 1 patient died)

LITERATURE SEARCHES

I. Analysis of data identified in the literature

Searches of bibliographic databases concerned the topics and types of studies that were defined in agreement with the project leader.

These searches were limited to publications in French, English, Italian and Spanish from the period January 2000 to July 2010.

The following sources were searched:
- for literature in French: Pascal database;
- for international literature: Medline and Embase databases.

The search was supplemented with the bibliography produced by the experts and with the references cited in the analysed documents.

II. Search strategy and results

The search strategy for the bibliographic databases was constructed using, for each topic, either terms from the thesaurus (descriptors) or free terms (from the title or abstract). These were combined with terms describing the types of studies.

The table in Appendix 2 presents the search strategy for the Medline, Pascal and Embase databases. In this table, the duplicate references can be presented within the different topics; for one given topic, there are no duplicates between the different types of studies.
This bibliographic search was conducted for the period January 2000 to the end of July 2010.

III. Dossiers submitted by the pharmaceutical companies

The distributors were requested to supply HAS with all clinical elements that would enable the reassessment of the AB and IAB of treatments for PAH.

DATA ON CLINICAL EFFICACY

New data from the dossiers submitted by the companies and/or from the literature search were integrated into one document. A critical reading of these data was performed so as to retain only those data, which appeared after the last opinion issued by the Committee, meta-analyses, systematic reviews of good-quality methodology and studies with a high level of evidence (phase III, randomised, comparative studies evaluating clinical endpoints and not surrogate endpoints such as haemodynamic parameters) conducted within the indications and at the dosages recommended by the marketing authorisation for the various proprietary products. In addition, cohort studies conducted with very small groups were not retained, neither were abstracts. A verification was performed to check that all the individual studies had been comprehensively covered in the available meta-analyses.

Therapeutic management is focused on a combination of various treatments (refer to therapeutic strategy). Numerous bibliographic data are available, which evaluate these treatment combinations, but which are not considered in this document because the indications in bitherapy have not been validated. Information from the SPCs for the various proprietary products is presented below:

- For TRACLEER: no clinical information concerning concomitant use with other treatments for PAH is available in the latest SPC.

- For VOLIBRIS: the SPC emphasises that efficacy has only been established in monotherapy.
Section 4.5 of the SPC states that "the efficacy and tolerance of VOLIBRIS during concomitant administration with other treatments for PAH (for example, prostanoids, type 5 phosphodiesterase inhibitors) have not been studied in controlled clinical trials in patients with PAH. Therefore, caution is recommended in the event of concomitant administration."

- For REVATIO: the SPC mentions the study of concomitant administration of sildenafil by the oral route and epoprostenol by injection.
Section 4.5 of the SPC states that "the efficacy and tolerance of sildenafil administered in combination with other treatments for PAH (for example, bosentan, iloprost) have not been studied in controlled clinical trials. Therefore, caution is recommended in cases of combined treatments."

- For ADCIRCA: section 4.4 of the SPC states that "the efficacy and tolerance of tadalafil administered in combination with prostacyclin or its analogues has not been studied in controlled clinical studies. Therefore, caution is recommended in the event of concomitant administration. The efficacy of tadalafil in patients who have already been treated with bosentan has not been demonstrated in a conclusive manner."
Section 4.5 of the SPC states that "the safety and efficacy of combining ADCIRCA with endothelin-1 receptor antagonists have not been studied."

- for REMODULIN - FLOLAN - VENTAVIS: no clinical information concerning concomitant use with other treatments for PAH is available in the latest SPC.

I. DATA SUBMITTED BY THE COMPANIES

I.1 Endothelin antagonists

I.1.1. TRACLEER

The company submitted studies enabling the marketing authorisation to be granted within the various therapeutic indications for TRACLEER as well as the results of its open-label follow-up. These studies have already been evaluated by the TC.
The company also supplied results of long-term, follow-up cohort studies. Due to the methodology of these studies, the conclusions must be interpreted with caution, however in the majority of them efficacy appears to be maintained in terms of improving the distance covered in the 6-minute walking test and in terms of survival rates of 95% after 1 year and 85% after 2 years in patients with idiopathic PAH functional class III.
In patients with PAH associated with connective tissue disease, the survival rate is approximately 85% after 1 year and 70% after 2 and 3 years.
The company also provided results from an open-label study evaluating the quality of life of 177 patients. From baseline to the 3rd month of treatment, the following parameters were significantly improved: physical activity, limitations due to physical condition, energy, social life, however, these results are exploratory.

I.1.2. VOLIBRIS

No new data are available since the last transparency Committee opinion of 16 July 2008. The company has supplied results of studies enabling the marketing authorisation to be granted; these have already been evaluated.

I.2 Phosphodiesterase inhibitors

I.2.1. REVATIO

No new data are available since the last transparency Committee opinion of 20 June 2007. The company has supplied results of a posteriori analyses of patient subgroups derived from studies which enabled the marketing authorisation to be granted (SUPER 1 and SUPER 2 studies); these have already been evaluated by the Committee.
The indication for this proprietary product was extended for patients in NYHA functional class II on 7 July 2009, on the basis of data from the SUPER 1 clinical study and its open-label extension phase, SUPER 2, which enabled an extension of the initial marketing authorisation for patients in functional class III. The SUPER 2 follow-up study was conducted using higher dosages than those recommended by the marketing authorisation (40 mg or 80 mg 3 times per day). These results cannot be taken into consideration by the Committee.
The results for patients in functional class II derive from an analysis of one subgroup, which was defined a posteriori. The analysis of data from the subgroup of patients in functional class II (n=103/277, namely 38% of patients) was not envisaged by the protocol and is only exploratory. The results are therefore presented for information purposes only.
After 12 weeks of treatment, the improvement in the distance covered in the 6-minute walking test in this subpopulation was 49.2 m (CI 95% [21.5; 76.97], p<0.001). This improvement was comparable to that observed with patients in functional class III.
Efficacy has not been formally demonstrated in patients in functional class II.
At baseline, the mean distance walked in 6 minutes by patients in functional class II was 379 ± 60 metres. According to the national French registry of patients with PAH[5], the distance walked is 415 ± 86 m for patients in functional class II and 319 ± 92 m for patients in functional class III.

[5] 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

The extent to which patients included in the study and considered to belong to functional class II are representative is questionable. In fact, the patients included and assigned to class II are more severely affected than those seen in practice and are near to being in class III.

I.2.2. ADCIRCA

The dossier was evaluated in July 2010. The conclusions of the Committee are summarised below.

"The efficacy and safety of tadalafil (ADCIRCA) in patients with PAH in functional classes II or III were evaluated in the LVGY placebo-controlled, randomised, double-blind, phase III study, which included 406 patients with PAH (82 in the placebo group, 79 in the group receiving tadalafil 40 mg, the recommended dosage in the marketing authorisation).

After 16 weeks of treatment, the difference of 26.0 m [9.5; 44.0] observed in comparison to placebo with respect to the criterion "distance covered in the 6-minute walking test" was statistically significant. However, this difference is modest and lower than the threshold of 35 m considered to be clinically relevant.

One of the therapeutic objectives in the management of PAH is the prevention of clinical deterioration. However, no conclusion can be drawn from the results obtained from analysis of the secondary criterion "interval to clinical exacerbation", due to its exploratory nature envisaged in the protocol. Furthermore, no statistically significant difference was observed between the tadalafil group and the placebo group with respect to the other secondary endpoints: change in WHO functional class, Borg dyspnoea index, with the exception of the quality of life. The effect on mortality is not known.

The efficacy of tadalafil in patients already treated with bosentan has not been demonstrated conclusively[6] whereas more than 50% of the included patients had been treated previously with bosentan.

The main adverse events were headaches and gastrointestinal complaints.

The tolerance profile appears similar to that observed for the other phosphodiesterase inhibitor, REVATIO.

This proprietary product is the subject of an RMP (risk management plan) and it should be noted that its prescription is restricted and treatment must be initiated and supervised exclusively by a physician who is experienced in the management of patients with PAH.

No data are available comparing it with an active comparator. A comparative study with TRACLEER, in particular, would have been possible given the dates of development of each of these proprietary products."

I.3 Prostacyclins

I.3.1. FLOLAN

No new data have been submitted by the company subsequent to the last opinion of the Committee on 8 June 2005. The company supplied studies which had already been available during previous evaluations.

I.3.2. VENTAVIS

The company supplied 2 new long-term, open-label, follow-up studies:

- the AIR II follow-up study covered a period of up to 5 years and evaluated monotherapy with iloprost. This was an extension phase of the study that enabled the marketing authorisation to be granted, namely a placebo-controlled study lasting 12 weeks, which had been examined by the Committee (see opinion of 7 April 2004);
- the STEP II study of tolerance over a period of 12 months, which evaluated iloprost in combination with bosentan. This study is not described since bitherapy does not

[6] This is a subgroup analysis. No method for adjustment on account of multiple comparisons was used. No formal conclusion can be drawn.

correspond to the indication in the marketing authorisation. It confirmed the tolerance profile that was already known for iloprost.

AIR II study, "Open-label, uncontrolled, long-term surveillance study of iloprost aerosol inhalation therapy in the treatment of patients with primary or secondary pulmonary hypertension".
Open-label study, the aim of which was to evaluate the long-term tolerance of iloprost in patients with primary or secondary PAH. This descriptive study is presented for information purposes only.
This study included 71 patients, including 33 with primary PAH (patients relevant for the indication in the marketing authorisation)[7]. The mean age of the patients was 55.2 +/- 11.1 years, 59.2% being in functional class III, 40.8% in functional class IV.
No endpoint was defined as the primary criterion.
The principal criteria evaluated were: functional class, overall survival, distance walked in the 6-minute test, quality of life.
The daily iloprost dosage was 15 to 45 micrograms/day, which is far higher than that recommended by the marketing authorisation, delivered in 6 to 9 inhalations per day.
Most of the results are available for the whole group of patients, and not for primary PAH, which is the only form of PAH covered by the marketing authorisation for this proprietary product.
The only available result for primary PAH is the survival rate, which was 88.2% after 1 year, 84.2% after 2 years and 64.4% after 5 years.

The most common adverse effects were congestive heart failure (26/71 of the patients in question), cough (23/71), peripheral oedema (17/71), bronchitis (14/71).
Of the 71 patients included, 56 discontinued iloprost treatment (25 patients due to inadequate efficacy, 10 due to serious adverse effects).

I.3.3. REMODULIN
The company supplied results from studies that had already been evaluated by the TC in its opinion of 20 July 2005.

New clinical data since the previous opinion:
• *Efficacy of subcutaneous Remodulin*[8]*:*
A randomised, open-label, placebo-controlled 8-week study in 22 patients (14 in the REMODULIN group, 8 in the placebo group), who were stable and had previously been treated with intravenous epoprostenol. The patients had idiopathic PAH, and were in functional class II (9 patients in the REMODULIN group, 3 in the placebo group) or functional class III (5 patients in the REMODULIN group, 4 in the placebo group)[9]. It should be noted that, in France, REMODULIN is indicated for patients in functional class III.
Clinical deterioration (no primary efficacy endpoint defined) was observed in 7 patients in the placebo group and 1 patient in the REMODULIN group ($p<0.05$).
The main adverse events were: pain at the injection site (13 patients treated with REMODULIN, 3 in the placebo group), erythema (10 patients treated with REMODULIN, none in the placebo group) and diarrhoea (7 patients in the REMODULIN group, 3 in the placebo group).
The results of this study should be interpreted with caution in view of its methodology, the short follow-up period and the small number of patients included.

[7] The other 38 patients had secondary PAH.
[8] M. RUBENFIRE et al. Transition from IV Epoprostenol to Subcutaneous Treprostinil in Pulmonary Arterial Hypertension. Chest 2007; 132: 757-763
[9] 1 patient was in functional class I.

• *Long-term efficacy of subcutaneous Remodulin*[10]*:*

Open-label retrospective study on the long-term follow-up of 122 patients (99 patients with idiopathic PAH (n=32) or PAH associated with congenital heart disease, 23 patients with chronic thromboembolic PAH (CTPAH), who were not eligible for surgery).
The majority of the included patients (66%) were in functional class III.
At 3 years, the test distance walked had changed from 305 ± 11 to 445 ± 12 metres. Survival was 88.6% at 1 year and 70.6% at 3 years.
Pain at the injection site was experienced by 82% of patients.
The results of this study should be interpreted with caution on account of its methodology.

• *Long-term results for patients treated with subcutaneous Remodulin*[11]*:*

Observational study lasting 4 years, which included 860 patients, of whom 423 had participated in placebo-controlled studies and had been treated with REMODULIN alone or in combination with another agent (105 patients had received bosentan, 25 sildenafil). PAH was idiopathic or associated with connective tissue disease in 48% of cases and 76% of patients were in functional class III.
Survival, the primary efficacy endpoint, was 87% at 1 year and 68% at 4 years for all patients.
For patients treated with REMODULIN monotherapy, the survival rate was 88% at 1 year and 70% at 4 years.
The most commonly reported adverse effect was pain at the injection site (92% of patients).
Treatment was discontinued due to adverse effects in 199 patients, and because of clinical deterioration in 117 patients.
The results of this study should be interpreted with caution on account of its methodology.

II. BIBLIOGRAPHICAL DATA

The majority of data retrieved concerned studies already evaluated by the Committee (these studies having been the subject of numerous publications with analyses by subgroup or *post hoc* analyses, or observational studies conducted on very small populations, or studies in which the indications or situations did not correspond to the current marketing authorisation. The most relevant of the studies and systematic reviews retrieved from the literature are presented below.
In a meta-analysis[12] of 11 controlled studies (1,457 patients) of short duration (3 to 6 months), it was observed that the distance covered in the 6-minute walking test increased by a mean of 33.7 metres, 95% CI [24.9; 42.5] with endothelin antagonists compared to placebo. The odds ratio for improvement in functional class was 1.6 [1.2; 2.1], while for deterioration in functional class it was 0.26 95% CI [0.16; 0.42]. No effect on mortality was demonstrated. The main adverse effect is hepatotoxicity. The data were exhaustively tested and the heterogeneity test was not significant.
This meta-analysis included one trial versus an active comparator, namely sildenafil. No difference in distance walked was observed between these 2 treatments. This is the only available result.

[10] I.Lang et al. Efficacy of Long-term Subcutaneous Treprostinil Sodium Therapy in Pulmonary Hypertension. Chest 2006; 129: 1636-1643
[11] R.J.Barst et al. Long-term Outcome in Pulmonary Arterial Hypertension Patients Treated With Subcutaneous Trepostinil. European Respiratory Journal. 2006; 28; 1195-1203.
[12] Liu C et al. endothelin receptor antagonists for pulmonary arterial hypertension. Cochrane database of systematic review 2009, issue 3.

A long-term (4 months) observational study[13] evaluated the efficacy, with respect to several endpoints, and the tolerance of bosentan used in PAH associated with systemic scleroderma. This was a prospective analysis of 49 patients, mainly in functional class III or IV. At 4 months, improvement in functional class and in haemodynamic parameters was observed in 16 patients with stabilisation after 1 year. No improvement in distance walked was observed. Overall survival was 80% at 1 year. Patients in this study had been previously treated with epoprostenol (n=14) or sildenafil (n=10).
Twenty-three patients died of cardiac failure subsequent to PAH.
In a retrospective study comparing two cohorts of patients with idiopathic PAH in functional class III, who received first-line treatment with epoprostenol or bosentan (Sitbon *et al.*, 2005), the survival at 3 years was found to be comparable for the two treatments. However, the number of patients followed-up for 3 years was smaller in the bosentan group. After 2 years, 25% of patients treated with bosentan required their treatment to be reinforced or replaced by another treatment (prostacyclin analogue or PDE-5 inhibitor).

A meta-analysis[14] evaluating the efficacy and tolerance of prostacyclins included 9 randomised and controlled trials, with a duration of between 3 days and 1 year and including 1,175 patients. The authors concluded that efficacy was shown by prostacyclins administered intravenously (improvement of 90 m in distance walked in the 6-minute test compared to conventional PAH treatment in 4 trials) or administered subcutaneously (median improvement of 16 m with treprostinil compared to placebo in 2 studies) and by inhaled prostacyclin (improvement of 36 m in one study versus placebo). However, the studies were of short duration and mostly included small numbers of patients.
The efficacy of different prostacyclins is variable. In the absence of studies comparing these different molecules, none of them can be recommended preferentially[15].

A meta-analysis[16] of all available controlled studies evaluating PAH treatments dating to 2005 included 16 studies with a mean duration of 13 weeks, which evaluated 1,962 patients in total, of whom 70% were in functional class III. No heterogeneity was found between the studies. No reduction in mortality from any cause was observed with the different treatments. All the treatments taken together showed a statistically significant increase in distance walked in the 6-minute test, but this increase is modest (42.8 m, 95% CI [27.8; 57.8], p<0.001).
This meta-analysis was updated[17] to include all recent controlled studies with the latest validated molecules. In total, 26 studies were included (n=3,462 patients). The results observed previously have been confirmed. No therapeutic class showed efficacy in terms of reducing mortality from any cause. The authors conclude that studies should be conducted, which will enable the clinical benefits of the treatments to be assessed. These should be long-term studies with more relevant endpoints.

A recent meta-analysis, including 21 clinical studies evaluating all treatments for PAH, showed a significant increase in distance walked and a decrease in mortality from all causes compared with placebo (of the order to 40%, RR=0.57 95% CI [0.35; 0.92] p=0.023) in 3,140

[13] D. Launay et al. Long term outcome of systemic sclerosis-associated pulmonary arterial hypertension treated with bosentan as first-line monotherapy followed or not by the addition of prostanoids or sildenafil. Rheumatology 2010; 49: 490-500
[14] Paramothayan NS et al. Prostacyclin for pulmonary hypertension in adults. Cochrane database of systematic reviews 2005, Issue 2.
[15] Kamal K. Mubarak. A review of prostaglandin analogs in the management of patients with pulmonary arterial hypertension. Respiratory Medicine 2010; 104: 9-21
[16] A. Macchia et al. A meta-analysis of trials of pulmonary hypertension: a clinical condition looking for drugs and research methodology. Am Heart J 2007; 153: 1037-47
[17] A. Macchia et al. Systematic review of trials using vasodilatators in pulmonary arterial hypertension: why a new approach is needed. Am Heart J 2010; 159: 245-257

patients[18]. Results by active substance or therapeutic class are not available. They are therefore limited and should be interpreted with caution.

A meta-analysis[19] including 24 studies (n=3,758 patients) evaluated all treatments with respect to the criterion of mortality from any cause. This meta-analysis showed a benefit in terms of survival for epoprostenol (RR of death from all causes =0.33 95% CI [0.13; 0.85]) non-significant heterogeneity test).
No effect was observed with all the other treatments.

The results of a cohort study following-up 354 patients (incident and prevalent cases) between October 2002 and October 2003, reported survival rates of 85.7% at 1 year, 69.6% at 2 years and 54.9% at 3 years[20]. Data from the French pulmonary hypertension registry[21,22], initiated on November 2006 and including 3,987 patients on 23 November 2010, showed that the survival rates of the patients had improved. Between 2006 and 2009, 751 cases of idiopathic PAH or PAH associated with a connective tissue disease were newly diagnosed (incident cases). The survival rate of these patients was 88.5% at 1 year, 78.2% at 2 years, 69.2% at 3 years.

[18] Galie N. et al. A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. Eur Heart J. 2009; 30: 394-403
[19] CJ Ryerson et al. Pharmacotherapy in pulmonary arterial hypertension: systematic review and meta-analysis. Respiratory Research 2010, 11:12
[20] M. Humbert et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. Circulation. 2010; 122: 156-163
[21] M. Humbert et al. Pulmonary arterial hypertension in France. Am J Respir Crit Care Med 2006; 173: 1023-1030
[22] M. Humert et al. Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. European Respiratory Journal. 2010, vol. 36, no3, pp. 549-555

TOLERANCE

I.1 Endothelin antagonists

I.1.1. TRACLEER

Postmarketing pharmacovigilance data for TRACLEER proprietary products derive from the last Periodic Safety Update Reports covering the period from 20 May 2009 to 19 November 2009. No new tolerance issues have been detected.

During the placebo-controlled studies, the most common dose-dependent adverse effects observed with bosentan were headache, hot flushes, disturbances in liver function, lower limb oedema, anaemia.

Treatment with bosentan is associated with dose-dependent increases in serum levels of liver aminotransferases, as a rule during the first 26 weeks of treatment. Their progression is slow and they frequently remain asymptomatic.

Since the product was placed on the market, most of the adverse effects reported have been similar to those reported during clinical studies. Rare cases of unexplained liver cirrhosis have been reported following prolonged treatment with TRACLEER in patients with multiple factors associated with comorbidities and polypharmacy. Rare cases of liver failure have also been reported. These cases reinforce the importance of monthly monitoring of liver function during the whole duration of treatment with TRACLEER.

5,000 patients were included into the postmarketing surveillance programme for TRACLEER PMS between May 2002 and November 2004. An increase in liver transaminases was reported in 352 patients, giving a gross incidence of 7.6%. Of these patients, 47% continued their treatment despite the occurrence of this adverse effect, which was observed during the first 6 months of treatment in most cases.

I.1.2. VOLIBRIS

Postmarketing pharmacovigilance data for VOLIBRIS derive from the last Periodic Safety Update Report covering the period from 15 June 2007 to 14 June 2010.

Respiratory problems (nasal congestion, sinusitis, rhinopharyngitis, rhinitis) and general problems (peripheral oedema, headache) represent the majority of adverse events reported.

The most commonly reported adverse effects, according to the SPC, are headache, peripheral oedema, fluid retention.

Since VOLIBRIS was placed onto the market, the following adverse events have been reported: vertigo, cardiac failure, syncope, hypotension, dyspnoea, nausea, vomiting, diarrhoea.

I.1.3. THELIN

The European and French health authorities were informed by the PFIZER company of the withdrawal of the proprietary product THELIN from the market internationally and the interruption of clinical trials underway on 10 December 2010. The decision was made by the company following the notification of three fatal cases of hepatic toxicity in England, India and Ukraine.

The hepatotoxic potential of THELIN became known after the drug received its marketing authorisation and became the object of strict surveillance. The SPC contains precise recommendations concerning contraindications and the manner of monitoring hepatic parameters in treated patients.

However, in view of the information available at present concerning the 3 fatal cases, it appears that in certain patients the hepatotoxicity can be unpredictable and irreversible, despite discontinuation of THELIN treatment. In view of the withdrawal of the marketing authorisation for this product, its reassessment by the Committee is not applicable.

TRACLEER and VOLIBRIS, 2 medicinal products from the same class, are also known for their adverse hepatic effects, the frequency and severity of which has not at present raised doubts about their use. They are, however, the object of strict surveillance. While awaiting the conclusions of the European reassessment of the hepatotoxicity of this class of medicinal products, the necessity of strictly keeping to the dosage recommendations and monitoring treated patients should be remembered.

I.2 Phosphodiesterase inhibitors

I.2.1. REVATIO

Postmarketing pharmacovigilance data for REVATIO derive from the last Periodic Safety Update Report (period from 1st November 2007 to 31 May 2008). During this period, a warning concerning a decrease or sudden loss of hearing (experienced with all phosphodiesterase inhibitors) was added to section 4.8, undesirable effects, of the SPC. A total of 127 cases (228 events) has been reported.
During placebo-controlled studies, the most commonly reported adverse effects (frequency equal to or greater than 10%) were headache, facial flushing, dyspepsia, diarrhoea and limb pain. They were generally mild to moderate in severity.
According to the SPC, visual abnormalities and cases of non-arteritic anterior ischaemic optic neuropathy have been reported following administration of sildenafil.

I.2.2. ADCIRCA

The main adverse events were headaches and gastrointestinal complaints.
The tolerance profile appears similar to that observed for the other phosphodiesterase inhibitor, REVATIO.

I.3 Prostacyclins

I.3.1. FLOLAN

Postmarketing pharmacovigilance data for FLOLAN derive from the last Periodic Safety Update Report (dated 31 March 2008).
Respiratory problems (dyspnoea, exacerbation of PAH associated with disease progression), general problems (asthenia, fever), reactions at the administration site, heart problems (heart failure, ventricular insufficiency, arrhythmia) and infections (catheter-associated septic events) form the majority of adverse events reported.
The most commonly reported adverse effects according to the SPC are headaches, facial flushing, nausea, vomiting, diarrhoea, jaw pain.

I.3.2. VENTAVIS

Postmarketing pharmacovigilance data for VENTAVIS derive from the last Periodic Safety Update Report covering the period from 16 September 2007 to 15 September 2008. The analysis of these data did not show any new risks, they agree with the risk data in the current market authorisation.
According to the SPC, since the product was marketed, nausea, vomiting, diarrhoea, dyspnoea and bronchospasm have been reported in patients treated with inhaled VENTAVIS.

According to the SPC, the adverse effects (increased coughing) result from local effects associated with administration by inhalation.
The most commonly reported adverse effects in clinical trials were vasodilation, hypotension, headaches and increased coughing.
Syncope and peripheral oedema are frequent manifestations of the disease itself, but they can also occur during treatment. An increase in their frequency should suggest disease exacerbation or lack of treatment efficacy.

I.3.3. REMODULIN

The adverse events reported since REMODULIN was placed onto the market are septicaemia, bacteraemia, local infection and abscess at the site of subcutaneous infusion. In addition, cases of generalised rash, sometimes with a macular or papular appearance, as well as cases of cellulitis have been reported rarely.
The SCP states that in clinical trials, as well as local effects associated with the administration of REMODULIN by subcutaneous infusion (local reaction, pain at the administration site), the most commonly reported adverse effects are headache, diarrhoea, nausea, skin eruptions, jaw pain, local reactions at the administration site: bleeding or haematoma).

CONCLUSIONS

The distance walked in the 6-minute test is the primary efficacy endpoint of all therapeutic placebo-controlled trials resulting in the marketing authorisation. This criterion is a simple way in which to assess the patient's functional handicap and exercise capacity, but it is subjective, because it is influenced by weight, height, gender and patient motivation. [23]
This endpoint is being more and more challenged in the literature. Some authors consider that it should be abandoned in the evaluation of PAH treatments[24] and that new primary efficacy endpoints should be evaluated in the studies, primarily the interval to clinical exacerbation, a composite criterion, which is judged to be the most relevant clinically, whereby it will be necessary to properly define the constituents (mortality due to any cause, hospital admissions, etc.)[11,25,26,27.] This criterion has frequently been evaluated as a secondary criterion in the trials that are available.
No relationship has been established between the evaluation of walking distance and morbidity-mortality[28]. It is a predictive factor that is independent of mortality and which does not permit it to be said whether the disease prognosis has improved.
In the majority of clinical trials, one of the chief limitations is that patients remain symptomatic with a non-optimum quality of life, despite the treatments[29]. The clinical benefit provided to patients by these different treatments is difficult to estimate.
It has not been demonstrated that the PAH treatments decrease mortality or delay disease progression. On the basis of intermediate criteria, the symptomatic benefit is modest. None of the proprietary products for treatment of PAH have shown an effect on survival in the controlled studies, with the exception of FLOLAN.

Endothelin antagonists:
- TRACLEER is the proprietary product with the most consistent clinical development, with 5 placebo-controlled trials. This is the only molecule for which a specific study has assessed patients with PAH in functional class II, and for which there exists widespread and long-term clinical experience (80,000 patients treated).
- for VOLIBRIS, there are long-term data deriving from an open-label follow-up lasting 2 years.

Phosphodiesterase inhibitors:
- for REVATIO, there are no long-term data for the recommended dose (20 mg 3 times per day), nor has any effect been demonstrated on prevention of clinical deterioration or survival. Practitioners consider that this dose may prove insufficient in certain patients. This

[23] Galie n. et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. The task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). European Heart Journal 2009; 30: 2493-2537
[24] A.J. Impens et al. The 6-minute walk test in scleroderma – how measuring everything measures nothing. Rheumatology 2008; 47: v68-v69
[25] Lewis Rubin and Gérald Simonneau. Perspective on the optimal endpoints for pulmonary arterial hypertension trials. Current Opinion in Pulmonary Medicine 2010; 16 (suppl 1): S43-S46
[26] N.Galie et al. Clinical worsening in trials of pulmonary arterial hypertension: results and implications. Current Opinion in Pulmonary Medicine 2010; 16 (suppl 1): S11-S19
[27] V. McLaughlin et al. end points and clinical trial design in pulmonary arterial hypertension. J. Am. Coll. Cardiol. 2009; 54: S97-S107
[28] A. Peacock et al. Endpoints in pulmonary arterial hypertension: the role of clinical worsening. Current Opinion in Pulmonary Medicine 2010; 16 (suppl 1): S1-S9
[29] Mc Laughlin et al. ACCCF/AHA 2009. Expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association Developed in Collaboration With the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. J. Am. Coll. Cardiol 2009; 53: 1573-1619.

proprietary product has no hepatotoxicity, but one of the limitations to its use is the optimum dose.

- for ADCIRCA, the only long-term data available cover 1 year.

Prostacyclins:
- for FLOLAN, a reduction in mortality has been observed[30]. This is the only proprietary product that has shown an effect on survival. This medicinal product is the reference treatment for the most severe forms of the disease, namely for patients in functional class IV.

- for VENTAVIS, the long-term results obtained are, unfortunately, somewhat disappointing (Opitz CF et al. Eur Heart J 2005).

- for REMODULIN, there are long-term data showing a positive impact on survival [10,11]. Its use in practice is very limited due to its cutaneous tolerability. In fact, pain at the injection site is observed in approximately 85% of patients and is responsible for discontinuation of treatment in approximately 40% of patients. This intolerance is dose-dependent. In practice, the dose used can be reduced, although sometimes insufficiently.

THERAPEUTIC STRATEGY

The objective of management is primarily to improve the patient's survival and quality of life.
Since PAH is a progressive disease over the short term, regular follow-up is necessary for early detection of clinical exacerbation and also to enable therapy to be escalated as soon as possible. Evaluation of the prognosis has an important place in the choice of initial treatment and in evaluation of the response to treatment[31].

The therapeutic strategy recommended by the transparency Committee in these opinions and found in the literature[32,33,34] is as follows:
Conventional treatment for PAH combines anticoagulants, diuretics, oxygen therapy, and calcium inhibitors.
In patients with PAH of class III in particular, the following can be used:
- by the oral route: endothelin antagonists (bosentan or ambrisentan) and phosphodiesterase inhibitors (sildenafil or tadalafil)
- by the inhalational route: iloprost (VENTAVIS), in cases of a contraindication to, or hepatic intolerance of, bosentan
- by the continuous subcutaneous route: treprostinil (REMODULIN), which can be offered for the same reasons as iloprost (VENTAVIS). The decision to embark on treprostinil therapy

[30] Barst RJ et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The primary pulmonary hypertension study group. N Engl J Med 1996; 334: 296-302.
Sitbon O et al. Long term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol 2002; 40: 780-8
[31] O. Sanchez et al. Diagnostic et prise en charge de l'hypertension pulmonaire en 2009. commentaires sur les nouvelles recommandations de l'European Society of Cardiology (ESC) et de l'European Respiratory Society (ERS). 2010, vol. 27, no2, pp. 141-150
[32] Mc Laughlin et al. ACCCF/AHA 2009. Expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association Developed in Collaboration With the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. J Am Coll Cardiol. 2009; 53/ 1573-1619.
[33] Avran Goldberg. Pulmonary Arterial Hypertension in Connective Tissues Diseases. Cardiology in Review. March/April 2010 - Volume 18 - Issue 2 - pp 85-88
[34] Joe R. Anderson et al. Pharmacotherapeutic Management of Pulmonary Arterial Hypertension. Cardiology in Review. May/June 2010 - Volume 18 - Issue 3 - pp 148-162

must take account of the high probability of it being necessary to persist with continuous subcutaneous infusion in the long term.

- by continuous infusion: epoprostenol (FLOLAN).

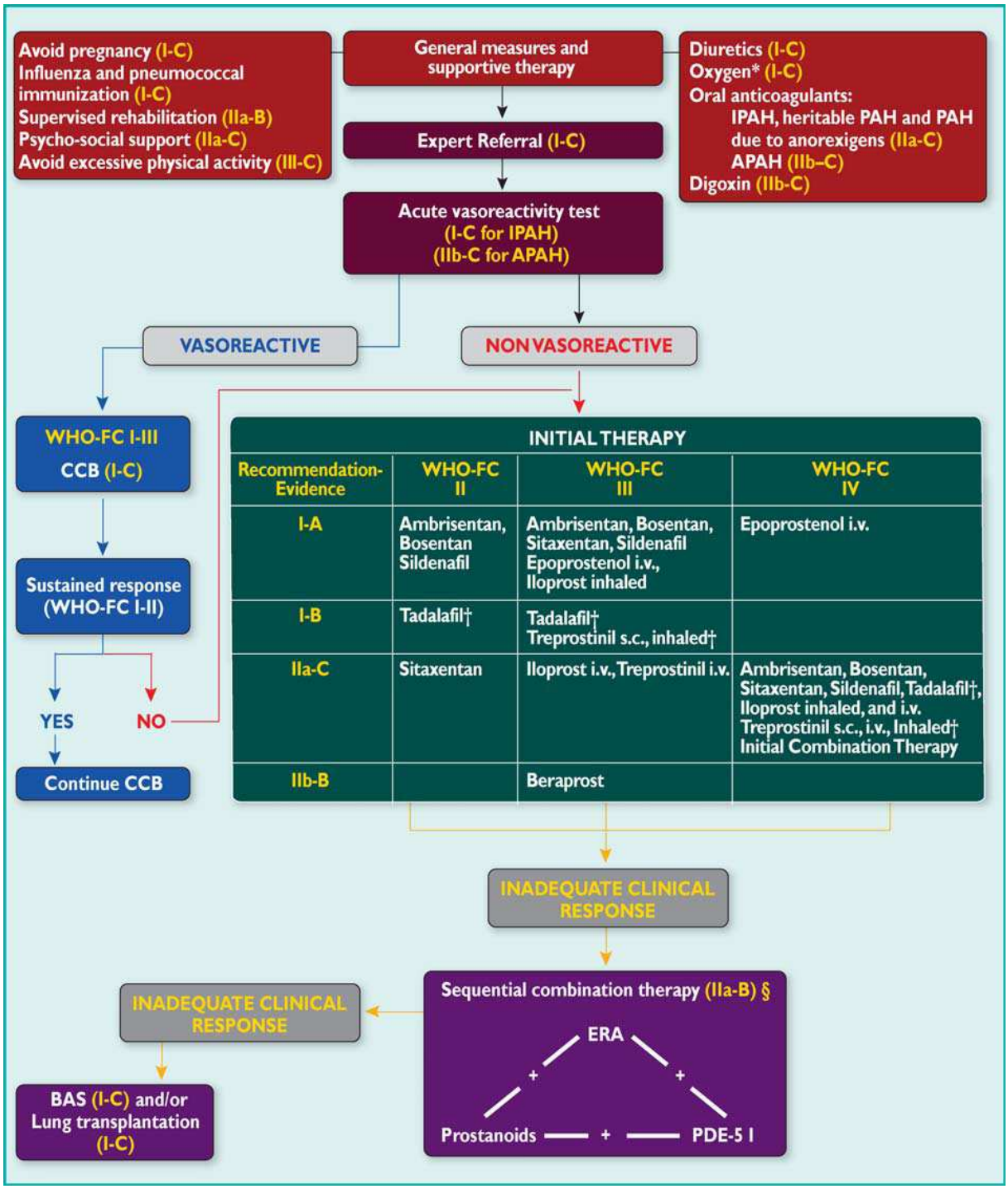
A lung or heart-and-lung transplant is the last-resort treatment. It is generally considered in patients who have not improved after 3 months of medical treatment.

The proprietary products TRACLEER, VOLIBRIS, ADCIRCA and REVATIO are indicated in the management of PAH in patients in functional class II.

The treatment is evaluated 3 to 4 months after its initiation. If the patient has achieved the therapeutic objectives established, the treatment is continued in association with regular follow-up by the centre of expertise.

It is important to emphasise the importance of regular follow-up of these patients, in order to monitor treatment efficacy or, on the other hand, exacerbation during treatment.

Treatment algorithm of the European Society of Cardiology and the European Society of Pneumology for idiopathic PAH associated with connective tissue disease[23]



The treatment algorithm recommended in the United States[35] is identical to that recommended in Europe, except for sitaxentan being recommended in grade B by the Americans for patients in functional classes II and III and iloprost being recommended in grade B for patients in functional class IV.

[35] Barst RJ et al. updated evidence-based treatment algorithm in pulmonary arterial hypertension. J Am Coll Cardiol 2009; 54: S78-S84

The conflicts of interests of the authors for these 2 recommendations are not announced in the publications.

Comments:
During treatment with an endothelin antagonist, it is necessary to determine liver enzymes prior to the start of treatment, two weeks after a change in dosage and then every month. The hepatic tolerance of bosentan was evaluated in more than 4,000 patients and increased transaminase levels were observed in 7.6% of cases, with discontinuation of treatment being justified in 3.2% of cases[36].
With bosentan, the risk of hepatic cytolysis is observed in 10% of cases, with ambrisentan this risk is approximately 2%.
The frequency with which an increase in transaminases is observed with ambrisentan is lower than that reported with bosentan, but regular monitoring is required.
According to the results of a study[37] conducted in 36 patients with PAH in functional class II or III, who stopped treatment with bosentan or sitaxentan due to elevated liver transaminases, ambrisentan can be a therapeutic option in cases of hepatic intolerance to other endothelin antagonists. However, the results of this study should be interpreted with caution, due to its methodology (open-label study, small number of patients, short follow-up period, etc) and due to the fact that at baseline 69.4% of patients were receiving treatment with prostacyclins and/or sildenafil, which is a therapeutic situation that has not been validated for the marketing authorisation.
In patients in functional class III or IV, treatment with intravenous prostacyclin results in significant improvement in functional and haemodynamic parameters. The results obtained with iloprost are, unfortunately, somewhat disappointing[38]. On the practical level, epoprostenol is a treatment that is complex to manage and restrictive for the patients (indwelling central venous catheter, twice-daily preparation of the product, portable pump). These are the inconveniences which led to the development of analogues administered subcutaneously or by inhalation. Treprostinil is administered subcutaneously and is associated very frequently with pain at the injection site (more than 85% of patients), which is the principal limiting factor for dose increases and results in discontinuation of treatment in 8% of cases. Iloprost has a short half-life, thus 6 to 9 inhalations per day are required, which is a disadvantage.

No data permits the therapeutic choice to be guided more towards one class than another in 1st line treatment. Nevertheless, in patients in functional class III, the prostacyclins are not used as first-line treatment although they have an marketing authorisation for this type of patient, but are administered following the failure of oral treatments.
In patients in functional class IV, epoprostenol (FLOLAN) is the reference treatment. This is the only treatment indicated in this population.

Several open-label studies suggest that a combination of these molecules could enable a synergistic therapeutic effect to be obtained. These combinations are currently used frequently in cases where monotherapy has failed. However these data are still limited and the place of bitherapies remains to be defined, particularly the choice of the therapeutic combination and the optimal time for its initiation[31] by means of trials satisfying current methodological requirements[39].

[36] Humbert M et al. Results of European post-marketing surveillance of bosentan in pulmonary hypertension. Eur Respir J 2007; 30: 338-44
[37] McGoon MD et al. Ambrisentan therapy in patients with pulmonary arterial hypertension who discontinued bosentan or sitaxentan due to liver function test abnormalities. Chest 2009; 135; 122-129
[38] D. Montani et al. Actualités thérapeutiques dans l'hypertension artérielle pulmonaire. AMC pratique. No.179. June 2009
[39] Teena Abraham et al. Role of combination therapy in the treatment of pulmonary arterial hypertension. Pharmacotherapy 2010; 30 (4): 390-404

However, combinations of treatments have originated from current practice in numerous centres of competence for PAH, despite the absence of efficacy and tolerance data over the short and long term[40]. They are suggested in cases of inadequate clinical response to monotherapy treatments (no improvement in functional class, clinical deterioration, clinical signs of right ventricular insufficiency, etc.).
According to the most recent recommendations, since no direct comparison between the treatments is available, none of them can be recommended preferentially as the 1st line treatment.

The optimum 1st line treatment in patients with systemic scleroderma remains a matter of controversy and more data are needed before one therapeutic class can be recommended[41].

No treatment apart from TRACLEER is recommended in children and patients under the age of 18. TRACLEER is the only treatment recommended for the treatment of PAH associated with left-to-right shunt congenital heart disease with Eisenmenger syndrome.

TARGET POPULATION

For VENTAVIS and REMODULIN:
Primary PAH is a rare disease affecting between 400 and 500 people in France.
Of these, approximately 60% would be in functional class III, this forming a target population of approximately 250 to 300 patients.
In this context, the population likely to benefit most from VENTAVIS or REMODULIN comprises patients with contraindications or hepatic intolerance to TRACLEER, for whom administration of FLOLAN by continuous intravenous injection is not appropriate. They represent approximately 10% of this population, namely a maximum of 50 patients.

For the other proprietary products:
The target population corresponds to patients:
- with idiopathic PAH
- with PAH associated with connective tissue disease
- in functional class II and III (NYHA classification).

The target population may be estimated from the following data:
- Idiopathic PAH is a rare disease affecting between 600 and 700 people in France. Of these, approximately 20% would be in NYHA class II, 60% in class III[42].
- PAH associated with connective tissues disease primarily concerns systemic scleroderma, systemic lupus erythematosus, dermatomyositis, mixed connective tissue disease and possibly rheumatoid arthritis.

The available data only enable the target population to be estimated with a large degree of uncertainty.
Of the 9,500 patients in France with systemic scleroderma (expert opinion), approximately 12% would have PAH, namely approximately 1,150 patients[43].

[40] Galie N. et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. The task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). European Heart Journal (2009) 30, 2493-2537
[41] Nadera J. Sweiss et al. Diagnosis and Management of Pulmonary Hypertension in Systemic Sclerosis. Curr Rheumatol Rep (2010) 12: 8-18
[42] 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
[43] 1,000 patients would have developed PAH associated with connective tissue disease in France in 2008. C. Agard et al. L'hypertension artérielle pulmonaire de la sclérodermie systémique en 2008. Journal des maladies vasculaires 2009; 34: 7-15

- Of the 50,000 patients with systemic lupus erythematosus (expert opinion), approximately 2.8% would have PAH, namely 1,400 patients.
- Of the 2,000 patients with mixed connective tissue disease, 15% (expert opinion) would have PAH, namely 300 patients.
Of these patients, approximately 25% would be in class II[44], 60% in functional class III[45].
On the basis of the above, the target population would be approximately 3,000 patients, with 2,000 of these in functional class III.

So far in France, approximately 4,000 patients are managed and recorded within the French registry for pulmonary hypertension.

USAGE DATA

GERS data at the hospital:

UCD [Common Dispensation and/or Distribution Unit] wording	Units sold in 2009
VOLIBRIS 5 mg	27 330
VOLIBRIS 10 mg	3 000
THELIN 100 mg	22 316
TRACLEER	Not available
REVATIO	1 968 390
VENTAVIS	141 060
FLOLAN 0.5 mg	185 713
FLOLAN 1.5 mg	115 465
REMODULIN 1 mg	29
REMODULIN 2.5 mg	464
REMODULIN 5 mg	590
REMODULIN 10 mg	58

[44] Humbert M et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med 2006;173: 1023-1030
[45] Mc Laughlin VV et al. Pulmonary arterial hypertension. Circulation 2006; 114: 1417-31

CONCLUSION
COMMITTEE RECOMMENDATIONS

I. Reassessment of actual benefit

PAH is a rare, life-threatening lung disease, which is characterised by progressive obstruction of small pulmonary arteries leading to a progressive increase in pulmonary arterial pressure and right cardiac insufficiency. PAH is defined as an increase, found on right cardiac catheterisation, in the mean pulmonary arterial pressure (PAPm) greater than or equal to 25 mmHg at rest without an increase in pulmonary capillary pressure. Asthenia, dyspnoea, chest pain, and loss of consciousness are the most common clinical signs. The median survival with symptomatic treatment is of the order of 2.5 years for patients with PAH in functional class III and 4.8 years for those with PAH in functional class II[46].

All treatments for PAH fall into the category of symptomatic treatments.

The efficacy/adverse effects ratio is moderate for all proprietary products apart from FLOLAN, for which it is classified as being high. The proprietary product THELIN has been withdrawn from the market following cases of fatal hepatotoxicity.

These medicinal products are first-line therapy. In practice, the prostacyclins are used as 2nd line, with the exception of FLOLAN, which is a 1st line treatment in patients with PAH in functional class IV, because it is the only treatment indicated for these severely affected patients, for whom no alternative medicinal treatment exists.

Public health benefit:

Although pulmonary arterial hypertension is a serious and life-threatening clinical situation, the public health burden of this disease is low due to the small number of patients concerned.

Improvement in the management of patients with pulmonary arterial hypertension is a public health need that has been listed as an identified priority (Law of 9 August 2004 on public health policy, Rare Disease Plan).

On the basis of updated available data, it is established that only epoprostenol (FLOLAN) has shown a benefit in terms of survival compared to conventional treatments in patients with PAH in functional classes III and IV. Bearing in mind the paucity of data other than exploratory data, which enable the impact on disease progression to be documented, the other proprietary products are not expected to have an impact, including one on the morbidity of treated patients.

However, a significant improvement in the quality of life has been observed over the short term with bosentan, ambrisentan[47], sildenafil and tadalafil.

In the absence of comparative data, no further distinctions can be made between the proprietary products.

In addition, no population-scale impact is expected on the morbidity-mortality and quality of life relating to this disease for any of the proprietary products other than FLOLAN, for which the expected impact is considered to be low.

Consequently, in the current state of knowledge, FLOLAN is expected to have a public health benefit. This benefit is slight. No public health benefit is expected with the other proprietary products.

The actual benefit is moderate for PAH treatments for all indications in their market authorisations, except in the case of FLOLAN, for which it is classed as high, and THELIN, the reassessment of which by the Committee is not applicable due to its withdrawal from the market following cases of fatal hepatotoxicity.

[46] D. Montani et al. Actualités thérapeutiques dans l'hypertension artérielle pulmonaire. AMC pratique. No.179. June 2009

[47] In the ARIES 2 study with the 5 mg dosage.

II. Reassessment of the improvement in actual benefit (IAB)

Given the known and demonstrated effect of FLOLAN on survival and its place in the therapeutic strategy, namely in patients with PAH in functional class IV, the transparency Committee considers that FLOLAN provides a substantial improvement in actual benefit (IAB II) in the management of patients with idiopathic PAH or PAH associated with connective tissue disease, who are in functional class III or IV.

In view of the available data and clinical experience, the transparency Committee considers that TRACLEER provides a moderate improvement in actual benefit (IAB III) in the management of idiopathic PAH or PAH associated with connective tissue disease or with congenital heart disease in patients in functional class II or III.

The transparency Committee considers that a minor improvement in actual benefit (IAB IV) is provided by the following proprietary products:
- VOLIBRIS, REVATIO and ADCIRCA in the treatment of idiopathic pulmonary arterial hypertension or PAH associated with systemic connective tissue disease in patients in functional class II or III,
- VENTAVIS and REMODULIN in the treatment of idiopathic pulmonary arterial hypertension in patients in functional class III.

The transparency Committee will reassess the proprietary products TRACLEER and VOLIBRIS in the light of the conclusions from the European evaluation of the hepatotoxicity of endothelin antagonists.

The transparency Committee, at the request of the Directorate-General for Health, wishes the orally administered proprietary products to be available in community pharmacies.

APPENDIX 1: Table 2: dosage and warnings

Proprietary products	Dosage	Special warnings and precautions for use
VENTAVIS	"Treatment with VENTAVIS should only be initiated and monitored by a doctor experienced in the management of pulmonary hypertension. VENTAVIS is intended to be administered by inhalation with the aid of a nebuliser. Adults: Dose per nebulisation session: the recommended dose for inhaled iloprost is: 2.5 micrograms or 5.0 micrograms (dose delivered at the nebuliser mouthpiece), starting with a low dose of 2.5 micrograms for the first inhalation, followed by 5 micrograms for the second inhalation. If the 5 microgram dose is poorly tolerated, it should be reduced to 2.5 micrograms. Studies on two compressed air nebulisers, HaloLite and Prodose, have shown them to have satisfactory nebulisation properties for the administration of VENTAVIS. The efficacy and tolerance of inhaled iloprost have not been established with other nebulisers which have different nebulisation properties. The nebulisation sessions are repeated 6 to 9 times a day, depending on the expected clinical effect and the patient's tolerance. Treatment duration depends on the patient's clinical condition and is established by the doctor. If the patient's clinical condition deteriorates despite this treatment, intravenous administration of prostacyclin should be considered. (Refer to SPC)"	"The use of VENTAVIS is not recommended in patients with unstable pulmonary hypertension and with advanced right cardiac insufficiency. In the event of deterioration or exacerbation of right cardiac insufficiency, a change to another treatment should be considered. In patients with low systemic blood pressure, caution is required in order to avoid increasing the risk of hypotension. Treatment with VENTAVIS should not be initiated in patients with a systolic blood pressure below 85 mmHg."
FLOLAN	"Recommended dosage in adults. - Acute vasodilation test: The only significance of this test is that it detects patients, who are responders to oral vasodilators (such as calcium inhibitors); it does not detect responders to epoprostenol administered over the long term (the indication for which is only justified in subjects who are non-responders in the acute test). It can easily be replaced by a test with inhaled nitric oxide (NO), which is simpler and without systemic effects. The product can be administered either by a peripheral or a central route. The infusion should be started at a level of 2 ng/kg/min, and then increased in steps of 2 ng/kg/min every 15 minutes or less frequently, until the appearance of limiting pharmacological effects, the most common of which are nausea, vomiting, headache, hypotension or tachycardia. As a guide, the mean maximum acute dose administered during clinical trials, which did not induce such effects, was 8.6 ± 0.3 ng/kg/min. - Continuous long-term infusion: for a long-term infusion, the diluted product is administered through a central venous catheter. The infusion rate of epoprostenol is adjusted under medical supervision. - *Initial dose*: The infusion should be started at a level of 1 ng/kg/min, and then increased in steps of 1 ng/kg/min every 12 to 24 hours, depending on tolerance, until a dosage of 10 ng/kg/min is reached. The dosage will then be increased by 1 ng/kg/min every 15 days up to a dose of 16 ng/kg/min. - *Adjustment of infused doses during long-term treatment*: the doses of epoprostenol are increased in accordance with relapses or exacerbation of PAH symptoms, as evidenced by a decrease in exercise tolerance in repeated walking tests (6 minutes) and by haemodynamic	"The decision to start treatment with FLOLAN should take into consideration the high probability that intravenous treatment will have to be maintained for a long period, possibly several years."

	parameters. If adverse events associated with overdose occur, consideration must be given to decreasing the epoprostenol doses. *- Methods and conditions for dose increase during long-term infusion* : the symptoms of PAH may recur gradually over the course of treatment. In general, they respond well to small increases in the epoprostenol dose. When the symptoms increase, the infusion dose is increased in steps of 1 ng/kg/min over sufficiently long intervals (1 to 4 weeks) to enable assessment of the clinical response. The infusion rates must be reassessed at regular intervals. As a guide, during clinical trials, the mean dose increase was 1 ng/kg/min per month, but this value showed considerable variation. *- Methods and conditions for dose reduction during long-term infusion :* the occurrence of clinical signs of overdose or of an excessive increase in cardiac output (dyspnoea, fatigue, weight loss, tachycardia, vomiting, etc) could require the dose of infused epoprostenol to be reduced. This phenomenon sometimes disappears without any dosage adjustment and it is often difficult to differentiate between these symptoms and signs suggestive of treatment inefficacy, hence the need for clinical and haemodynamic monitoring. The dose should be reduced gradually, in steps of 2 ng/kg/min every 15 minutes or longer, until the limiting effects disappear in relation to the dose administered. Sudden interruption of the epoprostenol infusion or a large and/or sudden decrease in infusion rate should be avoided due to the risk of occurrence of a life-threatening rebound effect. Use in the elderly, children, method of administration (refer to SPC)"	

REMODULIN	"REMODULIN is administered as a continuous subcutaneous infusion. The treatment should be initiated and monitored by a doctor experienced in the management of pulmonary hypertension. In adults: Initiation of treatment in patients not previously treated with prostacyclins: The treatment should be initiated under close medical supervision within a medical establishment with intensive care facilities. The recommended infusion rate at the initiation of treatment is 1.25 ng/kg/min. If this initial dose is poorly tolerated, the infusion rate should be reduced to 0.625 ng/kg/min. Dosage adjustments: The infusion rate is increased under medical supervision in steps of 1.25 ng/kg/min per week during the first four weeks of treatment, and then by 2.5 ng/kg/min per week. The dosage is adjusted individually under medical supervision in order to achieve a dose for long-term treatment that will ensure improvement of symptoms with a tolerability that is acceptable to the patient. In the principal studies lasting 12 weeks, efficacy was only maintained by increasing the dose 3 to 4 times per month on average. The objective of adjusting the dosage over the long term is to establish a dose at which improvement of PAH symptoms is achieved while minimising excessive pharmacodynamic effects. Adverse effects such as flushing, headache, hypotension, nausea, vomiting and diarrhoea are generally dependent on the dose of treprostinil administered. They can disappear when treatment is continued, but if they persist or the patient finds them intolerable, the infusion rate should be reduced so as to decrease their severity. During the follow-up phases of the clinical trials, the mean doses achieved were 26 ng/kg/min after 12 months of treatment, 36 ng/kg/min after 24 months and 42 ng/kg/min after 48 months. For the populations at risk, elderly patients, children and adolescents, refer to the SPC."	"The decision to embark on REMODULIN treatment must take account of the high probability of its being necessary to continue continuous subcutaneous infusion over a prolonged period. Thus it is appropriate to perform a careful assessment of the patient's ability to accept and monitor an indwelling catheter and infusion pump. Treprostinil is a powerful pulmonary and systemic vasodilator. In subjects with a low systemic blood pressure, treatment with treprostinil can increase the risk of hypotension. It is recommended that treatment should not be initiated in patients with a systolic blood pressure below 85 mmHg. The benefit of treatment with REMODULIN has not been established in patients with more severe stages of PAH (NYHA classification stage IV)."
VOLIBRIS	"The treatment should only be initiated by a doctor experienced in the treatment of pulmonary arterial hypertension. VOLIBRIS should be administered orally at a dose of 5 mg once per day. It is recommended that the tablet is swallowed whole, with or without a meal. It was possible to observe additional efficacy against symptoms when VOLIBRIS was used at a dose of 10 mg per day in patients in WHO functional class III, however an increase in peripheral oedema was also observed in these patients. The treatment of patients with pulmonary arterial hypertension associated with systemic collagen disease could require VOLIBRIS to be taken at a dose of 10 mg for optimum efficacy. In these patients, the 5 mg dose has to be well tolerated before considering an increase of the VOLIBRIS dose to 10 mg. The limited data available suggest that an abrupt discontinuation of VOLIBRIS is not associated with a rebound effect with exacerbation of PAH. Concerning use in elderly subjects, children, patients with renal and hepatic failure, refer to the SPC."	Not applicable
TRACLEER	The treatment should only be initiated and monitored by a doctor experienced in the management of pulmonary arterial hypertension. In adults, treatment with TRACLEER is initiated at a dosage of 62.5 mg twice daily for 4 weeks,	Serum levels of hepatic aminotransferases should therefore be determined before the start of treatment and then every month throughout treatment. In addition, the serum level of hepatic

	and the dosage is then increased until the maintenance dosage of 125 mg twice daily. No well-conducted controlled studies have been performed in children aged 2 years and older, which would enable establishment of the optimum maintenance dose. However, pharmacokinetic studies conducted in children have shown plasma concentrations of bosentan that were on average lower to those in adults, as well as the absence of augmentation when the dose of TRACLEER was increased to above 2 mg/kg twice daily. In view of these pharmacokinetic results, the higher doses appear to have a tendency to be more effective, and the possibility of an increased risk of adverse effects cannot be formally excluded in young children if the dosage is increased. No clinical study has been conducted to compare the benefit/risk ratio of 2 mg/kg with that of 4 mg/kg administered twice daily to children.	aminotransferases should be determined 2 weeks after any increase in dosage. In the event of clinical signs suggesting liver injury, the administration of TRACLEER must be discontinued and the treatment should not be repeated.
REVATIO	"REVATIO is intended for oral administration. The treatment should only be initiated and monitored by a doctor experienced in the management of pulmonary arterial hypertension. If the clinical condition deteriorates despite treatment with REVATIO, consideration should be given to alternative treatments. *Use in adults* The recommended dose is 20 mg three times daily. The tablets should be taken approximately every 6 to 8 hours with or without food. Use in the elderly, children and adolescents (refer to SPC)."	Not applicable
ADCIRCA	"The treatment should only be initiated and monitored by a physician experienced in the management of patients with pulmonary hypertension. The recommended dose is 40 mg (2x 20 mg) taken once daily dose with or without food. Use in patients with renal failure, patients with liver failure, children and adolescents (refer to SPC)	Not applicable

Appendix 2 : Literature search results

Type of study / Subject		Search period	Number of references found
	Terms used		
PULMONARY ARTERIAL HYPERTENSION			
Recommendations		Jan. 2000 – July 2010	72
Step 1	(pulmonary hypertension OR hypertension pulmonaire)/ti OR (hypertension, pulmonary OR pulmonary hypertension)/de		
AND			
Step 2	(guideline* OR recommendation*)/ti OR (guideline OR practice guideline OR consensus development conference, NIH OR consensus development conference)/dt OR (consensus conference* OR consensus statement*)/ti,ab OR consensus/ti		
Epidemiology		Jan. 2000 – July 2010	109
Step 1			
AND			
Step 3	(hypertension, pulmonary OR pulmonary hypertension)/epidemiology/de OR (epidemiol* OR prevalence OR incidence)/ti OR (prevalence OR incidence OR registries OR data collection OR health surveys OR incidence maladie OR registre OR register OR health survey)/de		
AND			
Step 4	(France OR french OR europ*)/ti,ab OR (Europe OR France)/de OR France/lieu_publication		
Natural history		Jan. 2000 – July 2010	61
Step 1			
AND			
Step 5	(natural history OR histoire naturelle)/ti,ab OR (course OR progression)/ti OR (disease progression OR age factors OR histoire naturelle)/de		
Treatment of PAH by AMBRISENTAN			
Meta-analyses / Systematic reviews		Jan. 2000 – July 2010	12
Step 1	(pulmonary hypertension OR hypertension pulmonaire)/titre OR		

	(hypertension, pulmonary OR pulmonary hypertension)/descripteur		
AND			
Step 6	ambrisentan/ti,ab OR ambrisentan/de OR volibris/ti,ab		
AND			
Step 7	metaanalys*/ti OR meta analys*/ti OR meta-analysis as topic/de OR meta-analysis/de OR metaanalysis/de OR meta-analysis/dt OR systematic* review*/ti,ab OR systematic review/de		
Other literature reviews		Jan. 2000 – July 2010	59
Step 1 AND Step 6			
AND			
Step 8	review/ti OR review/dt		
Randomised controlled studies		Jan. 2000 – July 2010	37
Step 1 AND Step 6			
AND			
Step 9	controlled clinical trials as topic/de OR controlled therapeutic trial/de OR randomized controlled trial/de OR randomized controlled trials as topic/de OR single-blind method/de OR single blind procedure/de OR double-blind method/de OR double blind procedure/de OR double blind study/de OR randomized controlled trial/ dt OR controlled clinical trial/dt OR random allocation/de OR randomization/de OR random*/ti		
Other clinical trials		Jan. 2000 – July 2010	173
Step 1 AND Step 6			
AND			
Step 10	cross-over studies/de OR crossover procedure/de OR crossover study/de OR clinical trial/de OR clinical trials as topic/de OR clinical trial/dt		
Cohort studies		Jan. 2000 – July 2010	2
Step 1 AND Step 6			
AND			
Step 11	cohort stud*/de OR cohort stud*/ti OR cohort analysis/de OR longitudinal stud*/de OR follow-up studies/de OR follow up/de OR follow up study/de OR prospective stud*/de		
Tolerance		Jan. 2000 – July 2010	24
Step 1 AND Step 6			
AND			
Step 12	safe*/ti OR unsafe*/ti,ab OR complication*/ti OR tolerance/ti OR adverse effect*/ti,ab OR adverse event*/ti,ab OR side effect*/ti,ab OR effet* secondaire*/ti,ab OR effet* indesirable*/ti,ab OR evenement*		

	indesirable*/ti,ab OR securite/ti,ab OR iatrogen*/ti,ab OR innocuit*/ti,ab OR iatrogenic disease/de OR iatrogenic/de OR pulmonary hypertension/adverse drug reaction/de OR pulmonary hypertension/side effect/de OR ambrisentan/drug toxicity/de OR ambrisentan/adverse drug reaction/de		
Treatment of PAH by BOSENTAN			
Meta-analyses / Systematic reviews		Jan. 2000 – July 2010	24
Step 1	(pulmonary hypertension OR hypertension pulmonaire)/titre OR (hypertension, pulmonary OR pulmonary hypertension)/descripteur		
AND			
Step 13	bosentan/ti,ab OR bosentan/de OR tracleer/ti,ab		
AND			
Step 7	metaanalys*/ti OR meta analys*/ti OR meta-analysis as topic/de OR meta-analysis/de OR metaanalysis/de OR meta-analysis/dt OR systematic* review*/ti,ab OR systematic review/de		
Other literature reviews		Jan. 2000 – July 2010	168
Step 1 AND Step 13			
AND			
Step 8	review/ti OR review/dt		
Randomised controlled studies		Jan. 2000 – July 2010	89
Step 1 AND Step 13			
AND			
Step 9	controlled clinical trials as topic/de OR controlled therapeutic trial/de OR randomized controlled trial/de OR randomized controlled trials as topic/de OR single-blind method/de OR single blind procedure/de OR double-blind method/de OR double blind procedure/de OR double blind study/de OR randomized controlled trial/ dt OR controlled clinical trial/dt OR random allocation/de OR randomization/de OR random*/ti		
Other clinical trials		Jan. 2000 – July 2010	237
Step 1 AND Step 13			
AND			
Step 10	cross-over studies/de OR crossover procedure/de OR crossover study/de OR clinical trial/de OR clinical trials as topic/de OR clinical trial/dt		
Cohort studies		Jan. 2000 –	57

		July 2010	
Step 1 AND Step 13			
AND			
Step 11	cohort stud*/de OR cohort stud*/ti OR cohort analysis/de OR longitudinal stud*/de OR follow-up studies/de OR follow up/de OR follow up study/de OR prospective stud*/de		
Tolerance		Jan. 2000 – July 2010	65
Step 1 AND Step 13			
AND			
Step 12	safe*/ti OR unsafe*/ti,ab OR complication*/ti OR tolerance/ti OR adverse effect*/ti,ab OR adverse event*/ti,ab OR side effect*/ti,ab OR effet* secondaire*/ti,ab OR effet* indesirable*/ti,ab OR evenement* indesirable*/ti,ab OR securite/ti,ab OR iatrogen*/ti,ab OR innocuit*/ti,ab OR iatrogenic disease/de OR iatrogenic/de OR pulmonary hypertension/adverse drug reaction/de OR pulmonary hypertension/side effect/de OR bosentan/drug toxicity/de OR bosentan/adverse drug reaction/de		
Treatment of PAH by EPOPROSTENOL			
Meta-analyses / Systematic reviews		Jan. 2000 – July 2010	13
Step 1	(pulmonary hypertension OR hypertension pulmonaire)/titre OR (hypertension, pulmonary OR pulmonary hypertension)/descripteur		
AND			
Step 14	epoprostenol/ti,ab OR epoprostenol/de OR flolan/ti,ab OR prostacyclin/de		
AND			
Step 7	metaanalys*/ti OR meta analys*/ti OR meta-analysis as topic/de OR meta-analysis/de OR metaanalysis/de OR meta-analysis/dt OR systematic* review*/ti,ab OR systematic review/de		
Other literature reviews		Jan. 2000 – July 2010	126
Step 1 AND Step 14			
AND			
Step 8	review/ti OR review/dt		
Randomised controlled studies		Jan. 2000 – July 2010	78
Step 1 AND Step 14			
AND			

Step 9	controlled clinical trials as topic/de OR controlled therapeutic trial/de OR randomized controlled trial/de OR randomized controlled trials as topic/de OR single-blind method/de OR single blind procedure/de OR double-blind method/de OR double blind procedure/de OR double blind study/de OR randomized controlled trial/ dt OR controlled clinical trial/dt OR random allocation/de OR randomization/de OR random*/ti		
Other clinical trials		Jan. 2000 – July 2010	130
Step 1 AND Step 14			
AND			
Step 10	cross-over studies/de OR crossover procedure/de OR crossover study/de OR clinical trial/de OR clinical trials as topic/de OR clinical trial/dt		
Cohort studies		Jan. 2000 – July 2010	79
Step 1 AND Step 14			
AND			
Step 11	cohort stud*/de OR cohort stud*/ti OR cohort analysis/de OR longitudinal stud*/de OR follow-up studies/de OR follow up/de OR follow up study/de OR prospective stud*/de		
Tolerance		Jan. 2000 – July 2010	90
Step 1 AND Step 14			
AND			
Step 12	safe*/ti OR unsafe*/ti,ab OR complication*/ti OR tolerance/ti OR adverse effect*/ti,ab OR adverse event*/ti,ab OR side effect*/ti,ab OR effet* secondaire*/ti,ab OR effet* indesirable*/ti,ab OR evenement* indesirable*/ti,ab OR securite/ti,ab OR iatrogen*/ti,ab OR innocuit*/ti,ab OR iatrogenic disease/de OR iatrogenic/de OR pulmonary hypertension/adverse drug reaction/de OR pulmonary hypertension/side effect/de OR prostacyclin/drug toxicity/de OR prostacyclin/adverse drug reaction/de OR epoprostenol/adverse effects/de		
Treatment of PAH by ILOPROST			
Meta-analyses / Systematic reviews		Jan. 2000 – July 2010	6
Step 1	(pulmonary hypertension OR hypertension pulmonaire)/titre OR (hypertension, pulmonary OR pulmonary hypertension)/descripteur		
AND			
Step 15	iloprost/ti,ab OR ciloprost/ti,ab OR iloprost/de OR ventavis/ti,ab		
AND			

Step 7	metaanalys*/ti OR meta analys*/ti OR meta-analysis as topic/de OR meta-analysis/de OR metaanalysis/de OR meta-analysis/dt OR systematic* review*/ti,ab OR systematic review/de		
Other literature reviews		Jan. 2000 – July 2010	111
Step 1 AND Step 15			
AND			
Step 8	review/ti OR review/dt		
Randomised controlled studies		Jan. 2000 – July 2010	50
Step 1 AND Step 15			
AND			
Step 9	controlled clinical trials as topic/de OR controlled therapeutic trial/de OR randomized controlled trial/de OR randomized controlled trials as topic/de OR single-blind method/de OR single blind procedure/de OR double-blind method/de OR double blind procedure/de OR double blind study/de OR randomized controlled trial/ dt OR controlled clinical trial/dt OR random allocation/de OR randomization/de OR random*/ti		
Other clinical trials		Jan. 2000 – July 2010	189
Step 1 AND Step 15			
AND			
Step 10	cross-over studies/de OR crossover procedure/de OR crossover study/de OR clinical trial/de OR clinical trials as topic/de OR clinical trial/dt		
Cohort studies		Jan. 2000 – July 2010	38
Step 1 AND Step 15			
AND			
Step 11	cohort stud*/de OR cohort stud*/ti OR cohort analysis/de OR longitudinal stud*/de OR follow-up studies/de OR follow up/de OR follow up study/de OR prospective stud*/de		
Tolerance		Jan. 2000 – July 2010	72
Step 1 AND Step 15			
AND			
Step 12	safe*/ti OR unsafe*/ti,ab OR complication*/ti OR tolerance/ti OR adverse effect*/ti,ab OR adverse event*/ti,ab OR side effect*/ti,ab OR effet* secondaire*/ti,ab OR effet* indesirable*/ti,ab OR evenement* indesirable*/ti,ab OR securite/ti,ab OR iatrogen*/ti,ab OR innocuit*/ti,ab OR iatrogenic disease/de OR iatrogenic/de OR pulmonary hypertension/adverse drug reaction/de OR pulmonary hypertension/side effect/de OR iloprost/drug toxicity/de OR iloprost/adverse drug reaction/de OR iloprost/adverse effects/de		

Treatment of PAH by SILDENAFIL			
Meta-analyses / Systematic reviews		Jan. 2000 – July 2010	13
Step 1	(pulmonary hypertension OR hypertension pulmonaire)/titre OR (hypertension, pulmonary OR pulmonary hypertension)/descripteur		
AND			
Step 16	sildenafil/ti,ab OR sildenafil/de OR revatio/ti,ab		
AND			
Step 7	metaanalys*/ti OR meta analys*/ti OR meta-analysis as topic/de OR meta-analysis/de OR metaanalysis/de OR meta-analysis/dt OR systematic* review*/ti,ab OR systematic review/de		
Other literature reviews		Jan. 2000 – July 2010	105
Step 1 AND Step 16			
AND			
Step 8	review/ti OR review/dt		
Randomised controlled studies		Jan. 2000 – July 2010	62
Step 1 AND Step 16			
AND			
Step 9	controlled clinical trials as topic/de OR controlled therapeutic trial/de OR randomized controlled trial/de OR randomized controlled trials as topic/de OR single-blind method/de OR single blind procedure/de OR double-blind method/de OR double blind procedure/de OR double blind study/de OR randomized controlled trial/ dt OR controlled clinical trial/dt OR random allocation/de OR randomization/de OR random*/ti		
Other clinical trials		Jan. 2000 – July 2010	85
Step 1 AND Step 16			
AND			
Step 10	cross-over studies/de OR crossover procedure/de OR crossover study/de OR clinical trial/de OR clinical trials as topic/de OR clinical trial/dt		
Cohort studies		Jan. 2000 – July 2010	30
Step 1 AND Step 16			
AND			
Step 11	cohort stud*/de OR cohort stud*/ti OR cohort analysis/de OR longitudinal		

	stud*/de OR follow-up studies/de OR follow up/de OR follow up study/de OR prospective stud*/de		
Tolerance		Jan. 2000 – July 2010	110
Step 1 AND Step 16			
AND			
Step 12	safe*/ti OR unsafe*/ti,ab OR complication*/ti OR tolerance/ti OR adverse effect*/ti,ab OR adverse event*/ti,ab OR side effect*/ti,ab OR effet* secondaire*/ti,ab OR effet* indesirable*/ti,ab OR evenement* indesirable*/ti,ab OR securite/ti,ab OR iatrogen*/ti,ab OR innocuit*/ti,ab OR iatrogenic disease/de OR iatrogenic/de OR pulmonary hypertension/adverse drug reaction/de OR pulmonary hypertension/side effect/de OR sildenafil/drug toxicity/de OR sildenafil/adverse drug reaction/de OR vasodilator agents/adverse effects/de OR phosphodiesterase inhibitors/adverse effects/de		
Treatment of PAH by SITAXENTAN			
Meta-analyses / Systematic reviews		Jan. 2000 – July 2010	17
Step 1	(pulmonary hypertension OR hypertension pulmonaire)/titre OR (hypertension, pulmonary OR pulmonary hypertension)/descripteur		
AND			
Step 17	sitaxentan/ti,ab OR sitaxsentan/ti,ab OR sitaxsentan/de OR thelin/ti,ab		
AND			
Step 7	metaanalys*/ti OR meta analys*/ti OR meta-analysis as topic/de OR meta-analysis/de OR metaanalysis/de OR meta-analysis/dt OR systematic* review*/ti,ab OR systematic review/de		
Other literature reviews		Jan. 2000 – July 2010	44
Step 1 AND Step 17			
AND			
Step 8	review/ti OR review/dt		
Randomised controlled studies		Jan. 2000 – July 2010	46
Step 1 AND Step 17			

AND			
Step 9	controlled clinical trials as topic/de OR controlled therapeutic trial/de OR randomized controlled trial/de OR randomized controlled trials as topic/de OR single-blind method/de OR single blind procedure/de OR double-blind method/de OR double blind procedure/de OR double blind study/de OR randomized controlled trial/ dt OR controlled clinical trial/dt OR random allocation/de OR randomization/de OR random*/ti		
Other clinical trials		Jan. 2000 – July 2010	94
Step 1 AND Step 17			
AND			
Step 10	cross-over studies/de OR crossover procedure/de OR crossover study/de OR clinical trial/de OR clinical trials as topic/de OR clinical trial/dt		
Cohort studies		Jan. 2000 – July 2010	18
Step 1 AND Step 17			
AND			
Step 11	cohort stud*/de OR cohort stud*/ti OR cohort analysis/de OR longitudinal stud*/de OR follow-up studies/de OR follow up/de OR follow up study/de OR prospective stud*/de		
Tolerance		Jan. 2000 – July 2010	11
Step 1 AND Step 17			
AND			
Step 12	safe*/ti OR unsafe*/ti,ab OR complication*/ti OR tolerance/ti OR adverse effect*/ti,ab OR adverse event*/ti,ab OR side effect*/ti,ab OR effet* secondaire*/ti,ab OR effet* indesirable*/ti,ab OR evenement* indesirable*/ti,ab OR securite/ti,ab OR iatrogen*/ti,ab OR innocuit*/ti,ab OR iatrogenic disease/de OR iatrogenic/de OR pulmonary hypertension/adverse drug reaction/de OR pulmonary hypertension/side effect/de OR sitaxsentan/drug toxicity/de OR sitaxsentan/adverse drug reaction/de		
Treatment of PAH by TADALAFIL			
Meta-analyses / Systematic reviews		Jan. 2000 – July 2010	5
Step 1	(pulmonary hypertension OR hypertension pulmonaire)/titre OR (hypertension, pulmonary OR pulmonary hypertension)/descripteur		
AND			
Step 18	tadalafil/ti,ab OR tadalafil/de OR cialis/ti,ab		
AND			

Step 7	metaanalys*/ti OR meta analys*/ti OR meta-analysis as topic/de OR meta-analysis/de OR metaanalysis/de OR meta-analysis/dt OR systematic* review*/ti,ab OR systematic review/de		
Other literature reviews		Jan. 2000 – July 2010	47
Step 1 AND Step 18			
AND			
Step 8	review/ti OR review/dt		
Randomised controlled studies		Jan. 2000 – July 2010	19
Step 1 AND Step 18			
AND			
Step 9	controlled clinical trials as topic/de OR controlled therapeutic trial/de OR randomized controlled trial/de OR randomized controlled trials as topic/de OR single-blind method/de OR single blind procedure/de OR double-blind method/de OR double blind procedure/de OR double blind study/de OR randomized controlled trial/ dt OR controlled clinical trial/dt OR random allocation/de OR randomization/de OR random*/ti		
Other clinical trials		Jan. 2000 – July 2010	83
Step 1 AND Step 18			
AND			
Step 10	cross-over studies/de OR crossover procedure/de OR crossover study/de OR clinical trial/de OR clinical trials as topic/de OR clinical trial/dt		
Cohort studies		Jan. 2000 – July 2010	5
Step 1 AND Step 18			
AND			
Step 11	cohort stud*/de OR cohort stud*/ti OR cohort analysis/de OR longitudinal stud*/de OR follow-up studies/de OR follow up/de OR follow up study/de OR prospective stud*/de		
Tolerance		Jan. 2000 – July 2010	9
Step 1 AND Step 18			
AND			
Step 12	safe*/ti OR unsafe*/ti,ab OR complication*/ti OR tolerance/ti OR adverse effect*/ti,ab OR adverse event*/ti,ab OR side effect*/ti,ab OR effet* secondaire*/ti,ab OR effet* indesirable*/ti,ab OR evenement* indesirable*/ti,ab OR securite/ti,ab OR iatrogen*/ti,ab OR innocuit*/ti,ab OR iatrogenic disease/de OR iatrogenic/de OR pulmonary hypertension/adverse drug reaction/de OR pulmonary hypertension/side effect/de OR tadalafil/drug toxicity/de OR tadalafil/adverse drug reaction/de		

Treatment of PAH by UNIPROST			
Meta-analyses / Systematic reviews		Jan. 2000 – July 2010	5
Step 1	(pulmonary hypertension OR hypertension pulmonaire)/titre OR (hypertension, pulmonary OR pulmonary hypertension)/descripteur		
AND			
Step 19	uniprost/ti,ab OR treprostinil/ti,ab OR uniprost/de OR remodulin/ti,ab		
AND			
Step 7	metaanalys*/ti OR meta analys*/ti OR meta-analysis as topic/de OR meta-analysis/de OR metaanalysis/de OR meta-analysis/dt OR systematic* review*/ti,ab OR systematic review/de		
Other literature reviews		Jan. 2000 – July 2010	35
Step 1 AND Step 19			
AND			
Step 8	review/ti OR review/dt		
Randomised controlled studies		Jan. 2000 – July 2010	28
Step 1 AND Step 19			
AND			
Step 9	controlled clinical trials as topic/de OR controlled therapeutic trial/de OR randomized controlled trial/de OR randomized controlled trials as topic/de OR single-blind method/de OR single blind procedure/de OR double-blind method/de OR double blind procedure/de OR double blind study/de OR randomized controlled trial/ dt OR controlled clinical trial/dt OR random allocation/de OR randomization/de OR random*/ti		
Other clinical trials		Jan. 2000 – July 2010	45
Step 1 AND Step 19			
AND			
Step 10	cross-over studies/de OR crossover procedure/de OR crossover study/de OR clinical trial/de OR clinical trials as topic/de OR clinical trial/dt		
Cohort studies		Jan. 2000 – July 2010	11
Step 1 AND Step 19			
AND			
Step 11	cohort stud*/de OR cohort stud*/ti OR cohort analysis/de OR longitudinal stud*/de OR follow-up studies/de OR follow up/de OR follow up study/de OR prospective stud*/de		

Tolerance		Jan. 2000 – July 2010	25
Step 1 AND Step 19			
AND			
Step 12	safe*/ti OR unsafe*/ti,ab OR complication*/ti OR tolerance/ti OR adverse effect*/ti,ab OR adverse event*/ti,ab OR side effect*/ti,ab OR effet* secondaire*/ti,ab OR effet* indesirable*/ti,ab OR evenement* indesirable*/ti,ab OR securite/ti,ab OR iatrogen*/ti,ab OR innocuit*/ti,ab OR iatrogenic disease/de OR iatrogenic/de OR pulmonary hypertension/adverse drug reaction/de OR pulmonary hypertension/side effect/de OR uniprost/drug toxicity/de OR uniprost/adverse drug reaction/de OR antihypertensive agents/adverse effects/de		