HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion
23 July 2014

ADEMPAS 0.5 mg, film-coated tablet
B/42 tablets (CIP: 34009 278 489 1 9)
ADEMPAS 1 mg, film-coated tablet
B/42 tablets (CIP: 34009 278 493 9 8)
B/90 tablets (CIP: 34009 278 495 1 0)
ADEMPAS 1.5 mg, film-coated tablet
B/42 tablets (CIP: 34009 278 496 8 8)
B/90 tablets (CIP: 34009 278 498 0 0)
ADEMPAS 2 mg, film-coated tablet
B/42 tablets (CIP: 34009 278 499 7 8)
B/90 tablets (CIP: 34009 278 501 1 0)
ADEMPAS 2.5 mg, film-coated tablet
B/42 tablets (CIP: 34009 278 502 8 8)
B/90 tablets (CIP: 34009 278 504 0 0)

Applicant: BAYER HEALTHCARE SAS

INN	riociguat
ATC code (2014)	C02KX05 (antihypertensives)
Reason for the request	**Inclusion**
List concerned	**Inclusion for hospital use (French Public Health Code L.5123-2)**
Indications concerned	**"Chronic thromboembolic pulmonary hypertension (CTEPH)** **ADEMPAS is indicated for the treatment of adult patients with WHO Functional Class II to III with** • **inoperable CTEPH,** • **persistent or recurrent CTEPH after surgical treatment,** **to improve exercise capacity.** **Pulmonary arterial hypertension (PAH)** **ADEMPAS, as monotherapy or in combination with endothelin receptor antagonists, is indicated for the treatment of adult patients with pulmonary arterial hypertension (PAH) with WHO Functional Class II to III to improve exercise capacity."**

Actual Benefit	- **Moderate in pulmonary arterial hypertension in functional class II to III in adult patients, as monotherapy or in combination with endothelin receptor antagonists, to improve exercise capacity.** - **Moderate in chronic thromboembolic pulmonary hypertension in functional class II to III which is inoperable, or persistent or recurrent after surgical treatment, to improve exercise capacity.**
Improvement in Actual Benefit	➢ **<u>Pulmonary arterial hypertension</u>** **The ADEMPAS proprietary medicinal products do not provide an improvement in actual benefit (level V, non-existent) in the management of pulmonary arterial hypertension in functional class II to III, in comparison with available specific treatments for pulmonary arterial hypertension.** ➢ **<u>Chronic thromboembolic pulmonary hypertension</u>** **The ADEMPAS proprietary medicinal products provide a minor improvement in actual benefit (level IV) in the management of chronic thromboembolic pulmonary hypertension in functional class II to III which is inoperable, or persistent or recurrent after surgical treatment, in the absence of any alternative treatment.**
Therapeutic use	➢ **<u>Pulmonary arterial hypertension</u>** **The efficacy of ADEMPAS has been demonstrated versus placebo through an improvement in 6-minute walk distance in the short and medium term, which is similar to the oral proprietary medicinal products indicated in PAH in functional class II to III. It should be noted that ADEMPAS cannot be used in combination with phosphodiesterase type 5 inhibitors, and that where there are risk factors such as recent episodes of serious haemoptysis, riociguat increases the risk of respiratory tract bleeding in these patients who are frequently taking anticoagulants.** **Taking account of these points, the ADEMPAS proprietary medicinal products form part of the specific symptomatic treatments available for class II PAH and class III PAH as a first-line therapy, as monotherapy or in combination with endothelin receptor antagonists only.** ➢ **<u>Chronic thromboembolic pulmonary hypertension</u>** **The efficacy of the ADEMPAS proprietary medicinal products, indicated in inoperable CTEPH or persistent or recurrent CTEPH after surgery, has been demonstrated versus placebo through an improvement in 6-minute walk distance in the short and medium term, in the absence of any available alternative treatments. From a safety point of view, it should be noted that where there are risk factors such as recent episodes of serious haemoptysis, riociguat increases the risk of respiratory tract bleeding in these patients who are frequently taking anticoagulants.** **Taking account of these points, the ADEMPAS proprietary medicinal products have a role in the symptomatic treatment of inoperable CTEPH or CTEPH that is persistent or recurrent after surgery.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Date initiated: 27 March 2014 (centralised procedure) For the CTEPH indication: Temporary authorisations for use by a named patient [*ATU nominative* in French] granted between 31 January and 25 March 2014 and temporary authorisation for use by a cohort since 24 February 2014 Undertakings in the context of the Marketing Authorisation: - Four-year international registry of patients with pulmonary arterial hypertension (indications selected: group 1 PAH and group 4 CTEPH) to assess the safety profile - Risk management plan
Prescribing and dispensing conditions/special status	Orphan medicinal product (date of designation: 20 December 2007) Medicine for hospital prescription Prescription restricted to certain specialists (Specialists in Pulmonology, Cardiology and Internal Medicine) Medicine requiring special monitoring

ATC Classification	2014	
	C	Cardiovascular system
	C02	Antihypertensives
	C02K	Other antihypertensives
	C02KX	Antihypertensives for pulmonary arterial hypertension
	C02KX05	riociguat

02 BACKGROUND

Application for inclusion of the proprietary medicinal product ADEMPAS on the list of medicines approved for hospital use.

ADEMPAS is an orphan drug. In inoperable chronic thromboembolic pulmonary hypertension (CTEPH) or CTEPH that persists or recurs after surgery, it has been granted four temporary authorisations for use by a named patient [ATU nominative in French] and has had temporary authorisation for use by a cohort (9 patients) since 24 February 2014.

Its active ingredient, riociguat, is a stimulator of soluble guanylate cyclase, the first in a novel class of specific treatment for pulmonary hypertension, which acts through the same pathway as phosphodiesterase type 5 inhibitors but intervenes at an earlier point.

03 THERAPEUTIC INDICATIONS

"Chronic thromboembolic pulmonary hypertension (CTEPH)
ADEMPAS is indicated for the treatment of adult patients with WHO Functional Class II to III with

- **inoperable CTEPH,**
- **persistent or recurrent CTEPH after surgical treatment,**

to improve exercise capacity.

Pulmonary arterial hypertension (PAH)
ADEMPAS, as monotherapy or in combination with endothelin receptor antagonists, is indicated for the treatment of adult patients with pulmonary arterial hypertension (PAH) with WHO Functional Class II to III to improve exercise capacity.
Efficacy has been shown in a PAH population including aetiologies of idiopathic or heritable PAH or PAH associated with connective tissue disease."

04 DOSAGE

"Treatment should only be initiated and monitored by a physician experienced in the treatment of CTEPH or PAH.

Posology

Dose titration
The recommended starting dose is 1 mg three times daily for 2 weeks. Tablets should be taken three times daily approximately 6 to 8 hours apart (see section 5.2 of SPC).

Dose should be increased by 0.5 mg three times daily every 2 weeks to a maximum of 2.5 mg three times daily, if systolic blood pressure is ≥ 95 mmHg and the patient has no signs or symptoms of hypotension. In some PAH patients, an adequate response on the 6-minute walk distance (6MWD) may be reached at a dose of 1.5 mg three times a day (see section 5.1).
If systolic blood pressure falls below 95 mmHg, the dose should be maintained provided the patient does not show any signs or symptoms of hypotension. If at any time during the up-titration phase systolic blood pressure decreases below 95 mmHg and the patient shows signs or symptoms of hypotension the current dose should be decreased by 0.5 mg three times daily.

Maintenance dose
The established individual dose should be maintained unless signs and symptoms of hypotension occur.
The maximum total daily dose is 7.5 mg, i.e. 2.5 mg 3 times daily.
If a dose is missed, treatment should be continued with the next dose as planned.
If not tolerated, dose reduction should be considered at any time.

Food
Tablets can generally be taken with or without food. For patients prone to hypotension, as a precautionary measure, switches between fed and fasted ADEMPAS intake are not recommended because of increased peak plasma levels of riociguat in fasting compared to the fed state.

Special populations

Individual dose titration at treatment initiation allows adjustment of the dose to the patient's needs.

Paediatric population
The safety and efficacy of riociguat in children and adolescents below 18 years have not been established. [...] Until more is known about the implications of these findings the use of riociguat in children and in growing adolescents should be avoided (see section 4.4 of SPC).

Elderly population
In elderly patients (65 years or older) there is a higher risk of hypotension and therefore particular care should be exercised during individual dose titration (see section 5.2 of SPC).

Hepatic impairment
Patients with severe hepatic impairment (Child Pugh C) have not been studied and therefore use of ADEMPAS is contraindicated in these patients (see section 4.3 of SPC).
Patients with moderate hepatic impairment (Child Pugh B) showed a higher exposure to this medicine (see section 5.2). Particular care should be exercised during individual dose titration in these patients.

Renal impairment
Data in patients with severe renal impairment (creatinine clearance < 30 ml/min) are limited and there are no data for patients on dialysis. Therefore use of ADEMPAS is not recommended in these patients (see section 4.4 of SPC).
Patients with moderate renal impairment (creatinine clearance < 50 to 30 ml/min) showed a higher exposure to this medicine (see section 5.2 of SPC). There is a higher risk of hypotension in patients with renal impairment, therefore particular care should be exercised during individual dose titration.

Smokers
Current smokers should be advised to stop smoking due to a risk of a lower response. Plasma concentrations of riociguat in smokers are reduced compared to non-smokers. A dose increase to the maximum daily dose of 2.5 mg three times daily may be required in patients who are smoking or start smoking during treatment (see section 4.5 and 5.2 of SPC).
A dose decrease may be required in patients who stop smoking."

05 THERAPEUTIC NEED

Pulmonary hypertension is classified into five groups, including.[1]

- pulmonary arterial hypertension (PAH), which can be idiopathic, heritable, drug or toxin-associated, or a complication of certain diseases (chronic respiratory diseases, connective tissue disease, congenital heart disease, portal hypertension, HIV infection, etc.);
- chronic thromboembolic pulmonary hypertension.

These two types of pulmonary hypertension are defined by a mean pulmonary artery pressure > 25 mmHg at rest, measured during right heart catheterisation, and a pre-capillary pressure ≥ 15 mmHg.[2,3]

Pulmonary arterial hypertension

Pulmonary arterial hypertension is a rare and serious pulmonary vascular disease defined as an increase in pulmonary arterial resistance leading to right-sided heart failure. Symptoms mainly occur on exertion and include dyspnoea, weakness, chest pain, presyncope and syncope. It has a prevalence of 15 cases per million adults.[4,5]

As well as a combination of several specific medicines and surgical procedures, the therapeutic management of pulmonary arterial hypertension includes general measures (sporting activities where possible, prevention of infections), associated treatments such as anticoagulants and diuretics, and oxygen therapy. The specific medicines used depend on arterial vasoreactivity (nitric oxide test during catheterisation) and on the severity of the disease according to the 1998 WHO functional classification (see Table 1).

The specific treatments recommended for class I to III PAH with arterial vasoreactivity are calcium channel blockers.[2] If there is no pulmonary arterial vasoreactivity or if calcium channel blockers fail, the treatments used are:

- prostacyclins (and analogues): epoprostenol, treprostinil, iloprost, beraprost
- endothelin receptor antagonists: bosentan, ambrisentan
- phosphodiesterase type 5 inhibitors: sildenafil, tadalafil

The treatment algorithm is described in Table 1.[2] If treatment fails again, a combination of therapies will be discussed. In cases of severe PAH that is insufficiently improved by maximum medical treatment, a lung transplant or endovascular atrial septostomy pending transplant may be alternative, last-resort therapies.[3]

In theory, the therapeutic needs of most patients with PAH are therefore covered by using these three classes of specific PAH treatments. Riociguat is a stimulator of soluble guanylate cyclase, the first in a novel class of specific symptomatic treatment for pulmonary hypertension, which acts through the same pathway as phosphodiesterase type 5 inhibitors but intervenes at an earlier point.

A response to treatment for pulmonary hypertension is indicated by an increase in the distance covered during the 6-minute walk test (> 380 or 440 m), a return to functional class I or II,

[1] Simonneau G, Gatzoulis MA, Adatia I et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2013; 62(25 Suppl): D34-41.

[2] Galie N, Hoeper M, Humbert M 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. Eur Heart J 2009; 30: 2493-537.

[3] Haute Autorité de Santé. Hypertension artérielle pulmonaire : Protocole national de diagnostic et de soins pour une maladie rare [Pulmonary arterial hypertension: National diagnosis and treatment protocol for a rare disease]. November 2007.

[4] Humbert M et al. Pulmonary Arterial Hypertension in France. Results from a national registry. Am J Respir Crit Care Med 2006; 173: 1023-30.

[5] Les cahiers d'Orphanet, série Maladies rares. Prévalence des maladies rares: données bibliographiques. 2013.

normalisation of haemodynamic and ultrasound parameters, NT-proBNP levels, and maximum oxygen consumption > 15 ml/min/kg.[6]

Table 1. Treatment algorithm according to WHO class for PAH and for a **negative** vasoreactivity test, based on the best level of evidence.

WHO functional class		Treatment
I	PAH with no functional limitations; normal physical activity does not lead to dyspnoea, excessive fatigue, chest pain or presyncope.	No treatment consensus
II	PAH with slight functional limitations; physical activity leads to dyspnoea, excessive fatigue, chest pain or presyncope. These patients have no symptoms at rest.	Ambrisentan, bosentan, sildenafil, tadalafil *Combination with other medicines from a different class may be discussed.*
III	PAH with significant functional limitations; even light physical activity leads to dyspnoea, excessive fatigue, chest pain or presyncope. These patients have no symptoms at rest.	Ambrisentan, bosentan, sildenafil, tadalafil **2nd-line treatments**: IV epoprostenol, inhaled iloprost, treprostinil *Combination with other medicines from a different class may be discussed.*
IV	PAH preventing any physical activity and/or with signs of right-sided heart failure. Dyspnoea and/or fatigue may occur even at rest. Disability is increased by any form of physical activity.	IV epoprostenol *Combination with other medicines from a different class may be discussed.*

Chronic thromboembolic pulmonary hypertension

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare but serious complication of venous thromboembolism, itself a common disease. CTEPH is characterised by persistent thrombi formed of organised tissue which obstruct the pulmonary arteries. The consequence of this obstruction is an increase in pulmonary vascular resistance resulting in pulmonary hypertension and progressive right-sided heart failure.

CTEPH is a rare disease with a prevalence of 3/100,000, but recent data suggest that it is under-diagnosed.[5,7] Patients usually present with progressive dyspnoea on exertion, with or without signs of right-sided heart failure (fatigue, palpitations, syncope or oedema). There is usually a period of a few months to a few years between the initial event (acute embolism) and the appearance of clinical signs (2 years for 3.8% of patients who have had a pulmonary embolism[5]).

Therapeutic management consists of supportive treatments such as long-term anticoagulants and specific treatments for pulmonary hypertension.[8] Pulmonary thromboendarterectomy is the treatment of choice whenever possible as it can restore near-normal cardiorespiratory function. Pulmonary angiography (together with right heart catheterisation) is used to determine the degree of haemodynamic impairment and to assess operability: thromboendarterectomy should be offered if there is a good correlation between the pulmonary vascular resistance (degree of pulmonary hypertension) and the anatomical obstruction (proximal or distal localisation and extent of thrombi).

When this procedure is not possible (distal lesions, comorbidities), lung or heart-lung transplantation may be considered. A recent technique, pulmonary angioplasty, is being developed and could be an alternative treatment in inoperable patients. Specific PAH treatments (see above)

[6] McLaughlin VV, Gaine SP, Howard LS et al. Treatment goals of pulmonary hypertension. J Am Coll Cardiol 2013; 25 Suppl: D73-81.

[7] McLaughlin VV, Archer S, Badesch D et al. ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension. J Am Coll Cardiol. 2009; 53: 1574-619.

[8] Wilkens H, Lang I, Behr J et al. Chronic thromboembolic pulmonary hypertension (CTEPH): Updated Recommendations of the Cologne Consensus Conference 2011. Int J Cardiol 2011; 154s: 54-60.

are also recommended in this situation, and in patients who have persistent or recurring symptoms following thromboendarterectomy. However, the data are limited and no therapies have been approved in the USA and Europe or been granted Marketing Authorisation in this indication.[2]

06 CLINICALLY RELEVANT COMPARATORS

06.1 In pulmonary arterial hypertension

6.1.1 Medicinal products

Medicines specifically indicated in the treatment of functional class II to III PAH, administered on top of supportive treatments (anticoagulants, diuretics, oxygen therapy), i.e.:

- endothelin receptor antagonists
- prostacyclin analogues (not used in the treatment of class II PAH)
- phosphodiesterase type 5 inhibitors.

1

NAME (INN) *Company*	Indication	Date of TC opinion	Actual Benefit	Improvement in Actual Benefit (Wording)	Reimbursed
Endothelin receptor antagonists					
TRACLEER (bosentan) *Actelion Pharmaceuticals France*	Treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO functional class III. Efficacy has been shown in: - Primary (idiopathic and familial) pulmonary arterial hypertension - Pulmonary arterial hypertension secondary to scleroderma without significant interstitial disease - Pulmonary arterial hypertension associated with congenital systemic-to-pulmonary shunts and Eisenmenger's physiology. Some improvements have also been shown in patients with pulmonary arterial hypertension (PAH) WHO functional class II.	05/01/2011 (PAH re-assessment)	Moderate	In view of the available data and clinical experience, the Transparency Committee considers that TRACLEER provides a moderate improvement in actual benefit (level 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.	**Yes (hospital use)**
VOLIBRIS (ambrisentan) *GlaxoSmithKline*	VOLIBRIS is indicated for the treatment of adult patients with pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease.	05/01/2011 (PAH re-assessment)	Moderate	The Transparency Committee considers that the VOLIBRIS proprietary medicinal products provide a minor improvement in actual benefit (level IV) in the treatment of idiopathic PAH or PAH associated with systemic collagen tissue disease in patients in functional class II or III.	**Yes (hospital use)**
Prostacyclin analogues					
REMODULIN (treprostinil) *Bioprojet Pharma*	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.	05/01/2011 (PAH re-assessment)	Moderate	The Transparency Committee considers that the REMODULIN proprietary medicinal products provide a minor improvement in actual benefit (level IV) in the treatment of idiopathic pulmonary arterial hypertension in patients in functional class III.	**Yes (hospital use)**
FLOLAN and generics (epoprostenol) *GlaxoSmithKline*	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 the severity scale of the New York Heart Association).	05/01/2011 (PAH re-assessment)	Substantial	Given the known and demonstrated effect of FLOLAN on survival and its role 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 (level II) in the management of patients with idiopathic PAH or PAH associated with connective tissue disease, who are in functional class III or IV.	**Yes (hospital use)**

NAME (INN) *Company*	Indication	Date of TC opinion	Actual Benefit	Improvement in Actual Benefit (Wording)	Reimbursed
VENTAVIS (iloprost) *Bayer HealthCare*	Treatment of adult patients with primary PAH, classified as functional class III, to improve exercise capacity and symptoms.	05/01/2011 (PAH re-assessment)	Moderate	The Transparency Committee considers that the proprietary medicinal product VENTAVIS provides a minor improvement in actual benefit (level IV) in the treatment of idiopathic pulmonary arterial hypertension in patients in functional class III.	**Yes (hospital use)**
Phosphodiesterase inhibitors					
REVATIO (sildenafil) *Pfizer*	Treatment of adult patients with pulmonary arterial hypertension classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease.	05/01/2011 (PAH re-assessment)	Moderate	The Transparency Committee considers that the proprietary medicinal product REVATIO provides a minor improvement in actual benefit (level IV) in the treatment of idiopathic PAH or PAH associated with systemic collagen tissue disease in patients in functional class II or III.	**Yes (hospital use)**
	Treatment of paediatric patients aged from 1 year to 17 years old with pulmonary arterial hypertension. Efficacy in terms of improvement of exercise capacity or pulmonary haemodynamics has been shown in primary pulmonary hypertension and pulmonary hypertension associated with congenital heart disease.	06/06/2012 (extension of the paediatric indication)	Moderate	The use of extemporaneous preparations made from sildenafil tablets is common in current clinical practice, and this is justified by the lack of treatment alternatives suitable for use in paediatrics. The pharmaceutical forms available and developed for the REVATIO proprietary medicinal products meet the quality and safety requirements for administration to children and adolescents. However, in the absence of data with a sufficient level of evidence, the Transparency Committee considers that: - REVATIO 20 mg, film-coated tablet, does not provide any improvement in actual benefit (level V) in the management of pulmonary arterial hypertension in children and adolescents aged from 1 to 17 years with PAH; - REVATIO 10 mg/ml, powder for oral suspension, is an addition to the range which is useful for the management of PAH in children and adolescents aged from 1 to 17 years with PAH and in adults unable to swallow film-coated tablets.	**Yes (hospital use)**
ADCIRCA (tadalafil) *Lilly France*	ADCIRCA is indicated in adults for the treatment of pulmonary arterial hypertension (PAH) classified as functional class II and III, to improve exercise capacity. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH related to collagen vascular disease.	05/01/2011 (PAH re-assessment)	Moderate	The Transparency Committee considers that the proprietary medicinal product ADCIRCA provides a minor improvement in actual benefit (level IV) in the treatment of idiopathic PAH or PAH associated with systemic collagen tissue disease in patients in functional class II or III.	**Yes (hospital use)**

6.1.2 Other health technologies

A lung transplant or endovascular atrial septostomy pending transplant may be offered as a last-resort therapy if the above treatments fail.

◗ Conclusion
The comparator medicines listed are all clinically relevant for this indication.

06.2 In chronic thromboembolic pulmonary hypertension

6.2.1 Medicinal products

In spite of the recommendations (see section “05. Therapeutic need”), none of the medicines listed above have Marketing Authorisation for the treatment of CTEPH, whether it is inoperable CTEPH or persistent/recurrent CTEPH after surgery.

6.2.2 Other health technologies

Not applicable.

◗ Conclusion
There are no comparators for this indication.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

The following table gives details of Marketing Authorisation and reimbursement in other countries.

Country	Date of MA	Marketing Authorisation	Reimbursed	
			Yes/No (date)	Population
Switzerland	22 Nov 2013	ADEMPAS is indicated in patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) and patients with persistent or recurrent CTEPH after surgical treatment to improve exercise capacity.	Yes 8 Oct 2013	Marketing Authorisation
USA	8 Oct 2013	ADEMPAS is a soluble guanylate cyclase (sGC) stimulator indicated for the treatment of adults with: • Persistent/recurrent chronic thromboembolic pulmonary hypertension (WHO Group 4) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO functional class. • Pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity and to delay clinical worsening. Efficacy was shown in patients on ADEMPAS monotherapy or in combination with endothelin receptor antagonists or prostacyclins. [...]	Yes 1 Jan 2014	Marketing Authorisation
Canada	19 Sept 2013	ADEMPAS (riociguat) is indicated for the treatment of: • inoperable CTEPH (WHO Group 4) • persistent or recurrent CTEPH after surgical treatment in adult patients (≥ 18 years of age) with WHO Functional Class II or III pulmonary hypertension. ADEMPAS should only be used by clinicians experienced in the diagnosis and treatment of CTEPH.	Yes 24 Apr 2014	Marketing Authorisation
	6 Mar 2014	Treatment of pulmonary arterial hypertension (PAH, WHO Group 1), as monotherapy or in combination with endothelin receptor antagonists, in adult patients (≥ 18 years of age) with WHO Functional Class II or III pulmonary hypertension.	Under assessment	
Japan	17 Jan 2014	Inoperable chronic thromboembolic pulmonary hypertension (CTEPH), or persistent or recurrent CTEPH after surgical treatment.	Yes March 2014	Marketing Authorisation (CTEPH)
Chile	27 Dec 2013	Pulmonary arterial hypertension (PAH) (WHO Group 1) in adults to improve exercise capacity, improve WHO functional class and delay clinical worsening. Persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH) (WHO Group 4) in adults after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO functional class.	Under assessment	
Australia	7 Apr 2014	ADEMPAS, as monotherapy or in combination with approved PAH treatments (endothelin receptor antagonists or inhaled or subcutaneous prostacyclins), is indicated for the treatment of: • idiopathic PAH • heritable PAH • PAH associated with connective tissue diseases • PAH associated with congenital heart disease in adult patients with WHO Functional Class II, III or IV symptoms. ADEMPAS is indicated for the treatment of: • persistent or recurrent CTEPH after surgical treatment or • inoperable CTEPH in adult patients with WHO Functional Class II, III or IV symptoms.	Under assessment	

08 ANALYSIS OF AVAILABLE DATA

The application for reimbursement of the ADEMPAS proprietary medicinal products is supported by data from:

- two phase III, double-blind, placebo-controlled studies: the PATENT-1 study (12934) for PAH and the CHEST-1 study (11348) for CTEPH;
- two ongoing open-label, non-comparative, follow-up studies: the PATENT-2 study (12935) and the CHEST-2 study (11349), which primarily aim to evaluate long-term safety in patients who have completed the PATENT-1 and CHEST-1 studies respectively.

It should be noted that the efficacy results from the non-comparative and open-label PATENT-2 and CHEST-2 studies come from an interim analysis, are descriptive in nature, and will not be detailed in this document.

08.1 Efficacy

8.1.1 In pulmonary arterial hypertension: PATENT-1 study

Methods

The PATENT-1 study is a multicentre,[9] double-blind, randomised, placebo-controlled study that was conducted between 2008 and 2012.

The primary objective was to compare the efficacy of riociguat 1.0-2.5 mg with placebo in patients with symptomatic PAH who were pre-treated with prostacyclin analogues (PAs) or endothelin receptor antagonists (ERAs) or were treatment-naive.

Patient selection criteria

The inclusion criteria were as follows:

- age between 18 and 80 years;
- symptomatic group 1 PAH (Venice classification[10]) as assessed by right heart catheterisation in the 6 previous weeks, which is idiopathic, familial, due to anorexigen or amphetamine use, or associated with connective tissue disease, congenital heart disease (surgical intervention more than 360 days ago) or portal hypertension with liver cirrhosis; the PAH should be characterised by:
  - distance covered on 6-minute walk test between 150 and 450 m;
  - pulmonary vascular resistance greater than 300 $dyn \cdot s \cdot cm^{-5}$;
  - mean pulmonary artery pressure greater than 25 mmHg;
- not pre-treated with ERAs or PAs or with no change to these treatments (ERAs or oral, inhaled or subcutaneous PAs) in the past 90 days;
- for patients on non-specific treatment: anticoagulants should have been started or changes to diuretic treatment made more than 30 days before inclusion and any changes to oxygen therapy should have been made more than 90 days before.

The main exclusion criteria were:

- pregnant or breast-feeding women;
- treatment with intravenous PAs, phosphodiesterase inhibitors or nitrates in the 90 days before inclusion;
- moderate to severe obstructive lung disease (maximum expiratory volume per second < 60%) or severe restrictive lung disease (total lung capacity < 70%);

[9] 124 centres including Europe (47% of inclusions), China, Australia, Japan, Singapore, South Korea, Taiwan, Thailand, Canada, USA, Argentina, Brazil, Mexico.

[10] The 2003 Venice classification incorporates persistent pulmonary hypertension of the newborn and PAH associated with veno-occlusive disease or pulmonary capillary haemangiomatosis, whereas the 2013 Nice classification separates out these elements under 1' and 1''.

- arterial blood gases before inclusion: SaO_2 < 88%, PaO_2 < 55mmHg, $PaCO_2$ > 45 mmHg;
- history in the past 90 days of uncontrolled hypertension or hypotension, atrial fibrillation or flutter, or left-sided heart failure (LVEF < 40%);
- heart rate below 50 or above 105 beats per minute on randomisation;
- pulmonary venous hypertension, hypertrophic obstructive cardiomyopathy, confirmed or suspected severe coronary disease, symptomatic atherosclerosis, valvular or myocardial disease (except for tricuspid regurgitation due to pulmonary hypertension);
- severe renal impairment or confirmed signs of hepatic impairment.

Treatments administered

An exploratory analysis was planned to evaluate the efficacy of riociguat at a maximum dose of 1.5 mg in the same population. Patients were therefore randomised to three treatment groups (4:2:1 randomisation stratified by ERA or AP pre-treatment status), specifically:

- riociguat 1.0-2.5 mg group with a dose of between 1.0 and 2.5 mg three times daily
- placebo group
- riociguat 1.0-1.5 mg group with a dose of between 1.0 and 1.5 mg three times daily.

Treatment was administered for 12 weeks and consisted of:

- an 8-week dose titration phase. For riociguat, the initial dose was 1.0 mg three times daily and this was adjusted in increments of 0.5 mg three times daily every 2 weeks depending on peripheral systolic blood pressure (SBP):
    - increase by 0.5 mg three times daily if SBP ≥ 95mmHg;
    - decrease by 0.5 mg three times daily if SBP ≤ 90 mmHg;
    - stop for 24 hours then restart with dose decreased by 0.5 mg three times daily if SBP ≤ 90 mmHg and there are clinical symptoms of hypotension;
- a 4-week maintenance phase, during which the riociguat dose could not be increased.

It should be noted that ERA or AP treatments could not be started in patients who were treatment-naive on inclusion, and could not be changed in patients who were already treated on inclusion.

Endpoints

The primary efficacy endpoint was the change in 6-minute walk distance from inclusion to week 12 of treatment.

The relevant secondary endpoints, at 12 weeks in relation to inclusion, were:

- change in PAH severity functional class (score indicating worsening or improvement by a certain number of classes);
- time to clinical worsening, defined as the time to occurrence of death (all-cause mortality), lung or heart transplant, atrial septostomy, or one of the following events associated with worsening PAH: hospitalisation, starting a specific treatment or adjusting pre-existing AP treatment, 6-minute walk distance reduced by more than 15% from inclusion or more than 30% from the previous visit, increase in severity according to functional class;
- change in pulmonary vascular resistance;
- change in NT-proBNP level;
- change in dyspnoea score on the Borg CR10 scale (measured at the end of the 6-minute walk test);
- change in quality of life scores (EQ-5D scale and Living with Pulmonary Hypertension Questionnaire).

Statistical analysis

The riociguat 1.0-2.5 mg group was compared with the placebo group in the intention-to-treat (ITT) population using an analysis of covariance (ANCOVA) adjusted for walk distance on inclusion, geographical region and the patient's ERA or AP naive/pre-treatment status. It should be noted that among the secondary endpoints, the score for change in functional class (severity) and the changes in dyspnoea scores (Borg CR10) were compared in the two groups using a stratified Wilcoxon test; times to clinical worsening were compared using a log-rank test (α risk=0.05).

Based on the hypothesis that there would be an absolute difference of 25 m in the walk test between the riociguat 1.0-2.5 mg group and the placebo group, with a standard deviation of 70 m,

for a power of 90% and an α risk of 5%, the number of subjects necessary was 250 patients in the riociguat 1.0-2.5 mg group and 125 patients in the placebo group.

Results

Exposure to treatment

Out of 445 patients included and randomised, 443 took the treatment at least once, namely 254 patients in the riociguat 1.0-2.5 mg group, 126 patients in the placebo group and 63 patients in the riociguat 1.0-1.5 mg group. 405 of the patients included received the treatment until the end of the trial. The mean durations of treatment and discontinuation rates were similar in all three treatment groups (Table 1).

Table 1. Exposure to treatment in the PATENT-1 study.

	Riociguat 2.5 mg N=254	**Placebo N=126**	**Riociguat 1.5 mg N=63**
Duration of treatment (days):			
Mean (standard deviation)	81.4 (15.6)	78.2 (20.5)	80.0 (18.6)
Median (range)	85.0 (1-97)	84.5 (1-94)	85.0 (12-96)
Treatment discontinuations:			
Total, *n (%)*	17 (6.7)	16 (12.6)	7 (10.9)
Due to adverse event, *n (%)*	8 (3.1)	7 (5.5)	1 (1.6)

Patient characteristics

The patient characteristics were comparable between the three treatment groups, with mostly women (79%). The mean age was 50.6 years (± 16.5) and a quarter of patients were aged 65 and over. About 6% of patients were smokers. The most common types of PAH in the patients included were idiopathic PAH (61.4%) followed by PAH associated with connective tissue disease (25.1%). The majority of patients (95%) had class II or III PAH (WHO functional classification), distributed as follows:

- class II: 42.5% in the riociguat 1.0-2.5 mg group versus 47.6% in the placebo group (and 30.2% in the riociguat 1.0-1.5 mg group);
- class III: 55.1% in the riociguat 1.0-2.5 mg group versus 46% in the placebo group (and 61.9% in the riociguat 1.0-1.5 mg group).

No difference in terms of functional classification was observed between the riociguat 1.0-2.5 mg group and the placebo group.

The distance covered on the 6-minute walk test was greater than or equal to 380 m for 45.2% of patients in the riociguat 1.0-2.5 mg group and 57.9% of patients in the placebo group.

About 26% of patients in the riociguat groups took calcium channel blockers during the study, versus 20% in the placebo group.

Efficacy on the primary endpoint

The mean change in 6-minute walk distance from inclusion to week 12 was +29.6 m in the riociguat 1.0-2.5 mg group and -5.6m in the placebo group (Table 2). The change in walk distance was greater in the riociguat 1.0-2.5 mg group than in the placebo group with an intergroup difference of 35.8 m (95% CI [20.1; 51.1]). The per-protocol analysis showed similar results.

Table 2. Change in distance covered in the 6-minute walk test at 12 weeks

Walk test (metres)	Riociguat 2.5 mg N=254	Placebo N=126	Riociguat 1.5 mg N=63
Intention-to-treat population			
On inclusion			
Mean (standard deviation)	**361.4 (67.7)**	**367.8 (74.6)**	**363.2 (66.6)**
Median (min-max)	**374.5 (160; 468)**	**391.0 (150; 450)**	**385.0 (158; 448)**
Change from inclusion to last visit			
Mean (standard deviation)	**29.6 (65.8)**	**-5.6 (85.5)**	**31.1 (79.3)**
Median (min-max)	**30.0 (-430; 279)**	**8.5 (-400; 204)**	**32.0 (-415; 190)**
Difference in least squares means (riociguat 2.5 – placebo)	**35.8**		
[95% CI]	**[20.1; 51.5]**		
p (ANCOVA)	**< 10^{-4}**		
Per-protocol population			
On inclusion			
Mean (standard deviation)	364.0 (65.2)	373.5 (69.0)	362.2 (69.0)
Median (min-max)	375.0 (160-450)	394.5 (155-450)	385.0 (158-448)
Change from inclusion to last visit			
Mean (standard deviation)	36.3 (55.7)	2.9 (73.0)	35.3 (81.5)
Median (min-max)	35.0 (-180-279)	12.0 (-348-204)	34.0 (-415-190)
Difference in least squares means (riociguat 2.5 – placebo)	33.52		
[95% CI]	[19.0; 48.0]		
p (ANCOVA)	**< 10^{-4}**		

Efficacy on the secondary endpoints

Functional class (indicating severity) was unchanged after 12 weeks for the majority of patients (75.6% of patients in the riociguat 1.0-2.5 mg group and 71.2% in the placebo group). The percentage of patients who moved to a less severe functional class was higher in the riociguat 1.0-2.5 mg group (20.5%) than in the placebo group (14.4%), and the percentage of patients who deteriorated into a more severe class was lower with 2.8% and 12.0% of patients respectively (p=0.003).

Clinical worsening of PAH (in conjunction with a clinical event) was found in three patients in the riociguat 1.0-2.5 mg group and in eight patients in the placebo group (p=0.005). Given the numbers involved, the usefulness of this comparison seems limited.

The reduction in pulmonary vascular resistance and in NT-proBNP levels between inclusion and week 12 was greater in the riociguat 1.0-2.5 mg group than in the placebo group (Table 3). These results should be interpreted in light of the substantial individual variability in these endpoints.

The change in dyspnoea score (Borg scale) was -0.4 in the riociguat 1.0-2.5 mg group and 0.1 in the placebo group at 12 weeks, from an initial score of 3.9 in both groups (p=0.002). Little difference was found in terms of quality of life.

Table 3. Change in secondary endpoints in the intention-to-treat population at 12 weeks.

Functional parameter	Riociguat 2.5 mg N=232	Placebo N=107	Riociguat 1.5 mg N=58
Pulmonary vascular resistance (dyn·s·cm^{-5})			
On inclusion, mean (standard deviation)	**791.0 (452.6)**	**834.1 (476.7)**	**847.8 (548.2)**
Change from inclusion to last visit, mean (SD)	**-223.3 (260.1)**	**-8.9 (316.6)**	**-167.8 (320.2)**
Difference in least squares means*	**-225.7**		
[95% CI]	**[-281.4; -170.1]**		
p (ANCOVA)	**< 10^{-4}**		
NT-proBNP level (pg/ml)			
On inclusion, mean (standard deviation)	**1026.7 (1799.2)**	**1228.1 (1774.9)**	**1189.7 (1404.7)**
Change from inclusion to last visit, mean (SD)	**-197.9 (1721.3)**	**232.4 (1011.1)**	**-471.5 (913.0)**
Difference in least squares means*	**-431.8**		
[95% CI]	**[-781.5; -82.1]**		
p (ANCOVA)	**0.01**		

* Difference (riociguat 1.0-2.5 mg – placebo).

8.1.2 In chronic thromboembolic pulmonary hypertension

Methods

The CHEST-1 study is a multicentre,[11] double-blind, randomised, placebo-controlled study that was conducted between 2009 and 2012.

The primary objective was to compare the efficacy of riociguat 1.0-2.5 mg with placebo in patients with inoperable CTEPH or persistent/recurrent CTEPH after pulmonary thromboendarterectomy.

Patient selection criteria

The inclusion criteria were as follows:

- age between 18 and 80 years;
- inoperable CTEPH diagnosed within the past 8 weeks:
  - 6-minute walk distance between 150 and 450 m
  - pulmonary vascular resistance greater than 300 $dyn \cdot s \cdot cm^{-5}$, measured at least 90 days after starting anticoagulant treatment
  - mean pulmonary artery pressure greater than 25 mmHg
- or persistent or recurrent CTEPH after thromboendarterectomy, with pulmonary vascular resistance greater than 300 $dyn \cdot s \cdot cm^{-5}$ measured at least 180 days after surgery;
- naive to specific treatment for pulmonary hypertension (ERAs, PAs or phosphodiesterase inhibitors);
- for patients on non-specific treatment: anticoagulants should have been started or changes to long-term oxygen therapy made more than 90 days before inclusion and any changes to diuretic treatment should have been made more than 30 days before.

The main exclusion criteria were:

- pregnant or breast-feeding women;
- pre-treatment with nitrates in the 90 days before inclusion;
- moderate to severe obstructive lung disease (maximum expiratory volume per second < 60%) or severe restrictive lung disease (total lung capacity < 70%);
- arterial blood gases before inclusion: SaO_2 < 88%, PaO_2 < 55mmHg, $PaCO_2$ > 45 mmHg;
- history in the past 90 days of uncontrolled hypertension or hypotension, atrial fibrillation or flutter, or left-sided heart failure (LVEF < 40%);
- heart rate below 50 or above 105 beats per minute on randomisation;
- pulmonary venous hypertension, hypertrophic obstructive cardiomyopathy, confirmed or suspected severe coronary disease, symptomatic atherosclerosis, valvular or myocardial disease (except for tricuspid regurgitation due to pulmonary hypertension);
- recurrent thromboembolism despite an appropriate oral anticoagulant treatment;
- severe renal impairment or confirmed signs of hepatic impairment.

Treatments administered

Patients were randomised to two treatment groups (2:1 randomisation):

- a riociguat group with a dose of between 1.0 and 2.5 mg three times daily;
- a placebo group.

Treatment was administered for 16 weeks and consisted of:

- an 8-week dose titration phase, as described for the previous study (PATENT-1);
- an 8-week maintenance phase, during which the riociguat dose could not be increased.

Endpoints

The primary efficacy endpoint was the change in 6-minute walk distance from inclusion to week 16 of treatment.

The relevant secondary endpoints, at 16 weeks in relation to inclusion, were:

- change in CTEPH severity functional class (score indicating worsening or improvement by a certain number of classes);

[11] 89 centres including Europe (60% of inclusions), China, Australia, Japan, South Korea, Taiwan, Thailand, Canada, USA, Argentina, Brazil, Mexico.

- time to clinical worsening, defined as the time to occurrence of death (all-cause mortality), lung or heart transplant, or one of the following events associated with worsening CTEPH: emergency thromboendarterectomy, hospitalisation, starting a specific treatment for pulmonary hypertension, persistent reduction in 6-minute walk distance by more than 15% from inclusion or more than 30% from the previous visit, increase in severity according to functional class;
- change in pulmonary vascular resistance;
- change in NT-proBNP level;
- change in dyspnoea score on the Borg CR10 scale (measured at the end of the 6-minute walk test);
- change in quality of life scores (EQ-5D scale and Living with Pulmonary Hypertension Questionnaire).

Statistical analysis

The riociguat group was compared with the placebo group in the intention-to-treat (ITT) population using an analysis of covariance (ANCOVA) adjusted for walk distance on inclusion and geographical region. It should be noted that among the secondary endpoints, the score for change in functional class (indicating severity) and the change in dyspnoea scores (Borg CR10) were compared in both groups using a stratified Wilcoxon test; times to clinical worsening were compared using a log-rank test (α risk=0.05).

Based on the hypothesis that there would be an absolute difference of 30 m in the walk test between the placebo group and the riociguat group, with a standard deviation of 70 m, for a power of 90% and an α risk of 5%, the number of subjects necessary was 174 patients in the riociguat group and 87 patients in the placebo group (2:1 randomisation design).

Results

Exposure to treatment

Out of 262 patients included and randomised, 261 took the treatment at least once, namely 173 patients in the riociguat group and 88 patients in the placebo group. 243 of the patients included received the treatment until the end of the trial. The mean durations of treatment and discontinuation rates were similar in both treatment groups (Table 4).

Table 4. Exposure to treatment in the CHEST-1 study.

	Riociguat N=173	**Placebo N=88**
Duration of treatment:		
Mean (standard deviation)	108.2 (21.2)	110.2 (14.8)
Median (range)	113.0 (2-130)	113.0 (14-126)
Treatment discontinuations:		
Total, *n (%)*	14 (8.0)	5 (5.7)
Due to adverse event, *n (%)*	4 (2.3)	2 (2.3)

Patient characteristics

The patient characteristics were comparable between the two treatment groups, with mostly women (65.9%). The mean age was 59.3 years (± 13.5) and 42.1% of subjects were aged 65 and over. About 4% of patients were smokers. 72.4% of the patients included had inoperable CTEPH and 27.6% had recurrent or persistent CTEPH after surgery, with no difference in distribution between the riociguat and placebo groups:

- inoperable CTEPH: 69.9% in the riociguat group versus 77.3% in the placebo group;
- recurrent or persistent CTEPH after surgery: 30.1% versus 22.7% respectively.

The majority of patients (95%) had class II or III PAH (WHO functional classification), distributed as follows:

- class II: 31.8% in the riociguat group versus 28.4% in the placebo group;
- class III: 61.8% versus 68.2% respectively.

No difference in terms of functional classification was observed between the riociguat group and the placebo group.

The distance covered on the 6-minute walk test was greater than or equal to 380 m for 37.0% of patients in the riociguat group and 43.2% of patients in the placebo group.
Between 19% and 20% of patients in each group took calcium channel blockers during the study.

Efficacy on the primary endpoint

The mean change in 6-minute walk distance from inclusion to week 16 was 38.9 m in the riociguat group and -5.5 m in the placebo group (Table 5). The change in walk distance was therefore greater in the riociguat group than in the placebo group with an intergroup difference of 45.7 m (95% CI [24.7; 66.6]). The per-protocol analysis showed similar results.
It should be noted that when analysing the primary efficacy endpoint in the subgroups “inoperable CTEPH” (n=189) and “postoperative CTEPH” (n=72), the change in walk distance was greater in the riociguat group than in the placebo group for the “inoperable CTEPH” subpopulation (intergroup difference: 53.9 m; 95% CI [28.5; 79.3]) but not for the “postoperative CTEPH” subpopulation (26.7 m; 95% CI [-9.7; 63.1]).

Table 5. Change in distance covered in the 6-minute walk test at 16 weeks

Walk distance (metres)	**Riociguat**	**Placebo**
Intention-to-treat population	**N=173**	**N=88**
On inclusion		
Mean (standard deviation)	342.3 (81.9)	356.0 (74.7)
Median (min-max)	360.0 (150-557)	372.0 (152-474)
Change from inclusion to last visit		
Mean (standard deviation)	38.9 (79.3)	-5.5 (84.3)
Median (min-max)	42.0 (-376-335)	5.0 (-389-226)
Difference in least squares means (riociguat 2.5 – placebo)	45.7	
[95% CI]	[24.7; 66.6]	
p (ANCOVA)	<0.0001	
Per-protocol population	**N=143**	**N=75**
On inclusion		
Mean (standard deviation)	345.6 (82.6)	356.6 (73.6)
Median (min-max)	362.0 (150-557)	372.0 (170-474)
Change from inclusion to last visit		
Mean (standard deviation)	45.5 (71.2)	-5.9 (88.4)
Median (min-max)	43.0 (-305-335)	6.0 (-389-226)
Difference in least squares means (riociguat 2.5 – placebo)	52.2	
[95% CI]	[30.5; 74.0]	
p (ANCOVA)	<0.0001	

Efficacy on the secondary endpoints

Functional class (indicating severity) was unchanged after 16 weeks for the majority of patients (61.8% of patients in the riociguat group and 78.2% in the placebo group). The percentage of patients who moved to a less severe functional class was higher in the riociguat group (30.6%) than in the placebo group (14.9%) (p=0.003).
Clinical worsening of PAH (in conjunction with a clinical event) occurred in four patients in the riociguat group and in five patients in the placebo group (p=0.17). Given the numbers involved, the usefulness of this comparison seems limited.
The reduction in pulmonary vascular resistance and in NT-proBNP levels between inclusion and week 16 was greater in the riociguat group than in the placebo group (Table 6).
The change in dyspnoea score (Borg scale) was -0.8 in the riociguat group and 0.2 in the placebo group at 16 weeks, from initial scores of 4.3 and 4.4 respectively (p=0.004). A slight improvement in quality of life scores was found with riociguat in comparison with placebo.

Table 6. Change in secondary endpoints in the intention-to-treat population at 16 weeks.

Functional parameter	Riociguat N=151	Placebo N=82
Pulmonary vascular resistance (dyn·s·cm^{-5})		
On inclusion, mean (standard deviation)	790.7 (431.6)	779.3 (400.9)
Change from inclusion to last visit, mean (SD)	-225.7 (247.5)	23.1 (273.5)
Difference in least squares means*	**-246.4**	
[95% CI]	**[-303.3; -189.5]**	
p (ANCOVA)	**<0.0001**	
NT-proBNP level (pg/mL)		
On inclusion, mean (standard deviation)	1508.3 (2337.8)	1705.8 (2567.2)
Change from inclusion to last visit, mean (SD)	-290.7 (1716.9)	76.4 (1446.6)
Difference in least squares means*	-444.0	
[95% CI]	[-843.0; -45.0]	
p (ANCOVA)	0.0293	

* Difference (riociguat 1.0-2.5 mg – placebo).

08.2 Safety/Adverse effects

8.2.1 Clinical study data

PATENT-1 study

In the PATENT-1 study, 317 patients received at least one dose of riociguat for a mean duration of 80 days. Out of 443 patients, 400 reported at least one adverse event (90.3%), with no difference between the treatment groups (90.6% in the riociguat 1.0-2.5 mg group, 88.1% in the placebo group and 93.7% in the riociguat 1.0-1.5 mg group).

These adverse events were of mild to moderate severity in 76% of cases.

The most common adverse events (> 5%) in this study were:

- gastrointestinal disorders: nausea (14.9%), dyspepsia (14.9%), diarrhoea (12.2%), vomiting (9.9%), gastro-oesophageal reflux (5.0%)
- nervous system disorders: headaches (25.7%), vertigo (15.8%)
- general disorders: peripheral oedema (16.3%), chest pain (7.4%)
- respiratory disorders: dyspnoea and epistaxis (7.7% each), cough (6.3%)
- cardiovascular disorders: palpitations (7.0%), hypotension (6.8%)
- nasopharyngitis (10.4%), insomnia (6.1%), anaemia (5.6%).

Adverse events were attributable to treatment in 60.3% of patients (Table 7).

The incidence of patients with serious adverse events was 11.4% in the riociguat 1.0-2.5 mg group, 17.5% in the riociguat 1.0-1.5 mg group and 18.3% in the placebo group. These were treatment-related in a total of 15 patients, namely eight in the riociguat 1.0-2.5 mg group (including three patients with syncope) and two in the riociguat 1.0-1.5 mg group.

Six patients died including three in the riociguat groups (septicaemias and haemoptysis).

Table 7. Incidence of the main treatment-related adverse events

	Riociguat 2.5 mg N=254	Placebo N=126	Riociguat 1.5 mg N=63
Headaches	51 (11.0)	19 (15.1)	15 (23.8)
Vertigo	26 (10.2)	12 (9.5)	11 (17.5)
Hypotension	22 (8.7)	2 (1.6)	2 (3.2)
Nausea	21 (8.3)	8 (6.3)	6 (9.5)
Vomiting	8 (3.1)	2 (1.6)	4 (6.3)
Diarrhoea	10 (3.9)	8 (6.3)	2 (3.2)
Peripheral oedema	10 (3.9)	4 (3.2)	5 (7.9)
Palpitations	13 (5.1)	3 (2.4)	2 (3.2)

PATENT-2 study

The PATENT-2 study is an open-label follow-up study that included patients who completed the PATENT-1 study from March 2009 onwards (study ongoing). All patients included were treated with riociguat 1.0-2.5 mg. Treatment included a new 8-week titration phase (maximum dose of 2.5 mg).

The safety data presented come from the interim analysis, involving patients included between March 2009 and February 2012. During this period, 363 patients received at least one dose of riociguat for a mean duration of 438 days, and 351 of these reported at least one adverse event (96.7%). The most common (> 5%) adverse events in this study (n=363) were:

- gastrointestinal disorders: diarrhoea (13.8%), nausea (12%), dyspepsia (10.8%), vomiting (10.5%), gastro-oesophageal reflux (5.5%), upper abdominal pain (5.0%)
- general disorders: peripheral oedema (17.9%), chest pain (9.4%), asthenia (6.1%)
- respiratory disorders: nasopharyngitis (19.8%), cough (14.3%), bronchitis, dyspnoea and epistaxis (9.1% each), pulmonary arterial hypertension (8.5%), upper respiratory tract infection (7.4%)
- cardiovascular disorders: hypotension (7.2%), palpitations (5.8%), ventricular failure (5.0%)
- musculoskeletal disorders: back pain (7.4%), joint pain (6.3%)
- nervous system disorders: vertigo (18.5%), headaches (16.5%), syncope (5.5%)
- anaemia (7.4%), hypokalaemia (6.3%), insomnia (6.1%).

Treatment was stopped as a result of these adverse events in 7.7% of patients (n=28) and was mild to moderate in severity in 75% of cases.

Adverse events could be attributed to riociguat in 51% of patients and the most common (≥ 3 %) of these were diarrhoea (3.3%), dyspepsia (6.9%), nausea (4.4%), peripheral oedema (3.9%), vertigo (8.3%), headaches (8.3%) and hypotension (5.2%).

The incidence of patients with serious adverse events was 38.6% (n=140), primarily PAH (6.9%), right ventricular failure (3.9%) and syncope (5.5%). These were treatment-related in 17 patients, primarily syncope (n=5, 1.4%).

Nineteen patients died, with two deaths related to riociguat (haemoptysis and pulmonary arterial hypertension).

CHEST-1 study

In the CHEST-1 study, 173 patients received at least one dose of riociguat for a mean duration of 108 days. 160 patients reported at least one adverse event (92.5%), with no difference between the treatment groups (91.9% in the riociguat group and 86.4% in the placebo group). These adverse events were of mild to moderate severity in 89% of cases.

The most common adverse events (≥ 5%) in this study were:

- gastrointestinal disorders: dyspepsia (13.4%), nausea (10.0%), diarrhoea (8.0%), vomiting (7.7%)
- nervous system disorders: headaches (21.8%), vertigo (19.2%)
- respiratory disorders: cough (9.6%), dyspnoea (7.7%), upper respiratory tract infection (5.4%)
- hypotension (7.3%)
- peripheral oedema (18.8%)

- nasopharyngitis (13.0%).

Treatment was stopped as a result of these adverse events in seven patients, including five in the riociguat group.
The adverse events could be attributed to treatment in 59.5% of patients in the riociguat group versus 40.9% in the placebo group (Table 8).
The percentage of patients with serious adverse events was 19.7% in the riociguat group versus 18.3% in the placebo group. These were treatment-related in seven patients, including six in the riociguat group (three patients had syncope).
Five patients died including two in the riociguat group (heart failure and acute kidney injury/catheter site haemorrhage).

Table 8. Incidence of the treatment-related adverse events per treatment group

	Riociguat N=173	**Placebo N=88**
Headaches	27 (15.6)	7 (8.0)
Vertigo	26 (15.0)	3 (3.4)
Dyspepsia	21 (12.1)	6 (6.8)
Hypotension	14 (8.1)	0
Nausea	11 (6.4)	5 (5.7)
Peripheral oedema	5 (2.9)	8 (9.1)

CHEST-2 study

The CHEST-2 study is a multicentre, open-label follow-up study that included patients who completed the CHEST-1 study from July 2009 onwards (study ongoing). All patients included were treated with riociguat 1.0-2.5 mg. Treatment included a new 8-week titration phase.
The safety data presented come from the interim analysis, involving patients included between July 2009 and March 2012. During this period, 194 patients received at least one dose of riociguat for a mean duration of about 388 days, of whom 180 reported at least one adverse event (92.8%). The most common adverse events (> 5%) in this study were:

- gastrointestinal disorders: diarrhoea (11.9%), dyspepsia (9.8%), nausea (7.7%)
- general disorders: peripheral oedema (15.5%), chest pain (6.2%)
- infections: nasopharyngitis (21.6%), bronchitis (7.2%), upper respiratory tract infection (7.7%)
- respiratory disorders: cough (9.8%), dyspnoea (8.2%), epistaxis (5.2%), pulmonary hypertension (5.2%)
- cardiovascular disorders: hypotension (5.7%), palpitations (5.7%), ventricular failure (5.2%)
- musculoskeletal disorders: back pain (8.8%), joint pain (8.2%), muscle spasms (5.2%)
- nervous system disorders: vertigo (17.0%), headaches (5.2%), syncope (7.7%)

Treatment was stopped as a result of these adverse events in three patients including two in the riociguat group (psychiatric decompensation and pulmonary arterial hypertension) and was mild to moderate in severity in 83% of cases.

Adverse events could be attributed to riociguat in 42.8% of patients and the most common (≥ 3 %) of these were vertigo (8.2%), dyspepsia (7.2%), hypotension (5.7%) and headaches (3.1%).

The percentage of patients with serious adverse events was 30.4% (n=59), primarily pulmonary hypertension (3.6%), right ventricular failure (4.6%) and syncope (5.2%). These events were related to riociguat in eight patients (4.4%), primarily hypotension (n=2, 1.6%).
Five patients died following a serious adverse event including one cardiac arrest (n=3).

8.2.2 SPC data

The safety data in the SPC come from the phase III trials conducted.
The adverse effects identified, listed by frequency, were as follows:

- Very common (≥ 10%): dizziness, headaches, dyspepsia, diarrhoea, nausea, vomiting, peripheral oedema;

- Common (≥ 1%, < 10%): infectious gastroenteritis, anaemia, palpitations, hypotension, haemoptysis, epistaxis, nasal congestion, gastritis, gastro-oesophageal reflux, dysphagia, gastrointestinal and abdominal pains, constipation, abdominal distension;
- Uncommon (≥ 1/1000, < 1%): pulmonary haemorrhage.

08.3 Summary & discussion

In the indication class II or III pulmonary arterial hypertension (PAH) (as monotherapy or in combination with endothelin receptor antagonists), the application for inclusion of the ADEMPAS proprietary medicinal products is supported by the PATENT-1 study, a randomised, double-blind, phase III study comparing the efficacy of riociguat at a maximum dose of 2.5 mg with placebo, in this population and for a period of 12 weeks, including 8 weeks of dose titration.
The 443 patients included and treated were aged 50 years on average and most commonly had idiopathic PAH or PAH associated with connective tissue disease, in functional class II or III (95% of patients). They were randomised to three groups following a 4:2:1 randomisation design (stratified by prostacyclin analogue or endothelin receptor antagonist naive/pre-treatment status): riociguat 1.0-2.5 mg (n=254), placebo (n=126) and riociguat 1.0-1.5 mg (n=63, group defined as for exploratory purposes).
The primary efficacy endpoint was change in the 6-minute walk distance at 12 weeks, which was greater in the riociguat 1.0-2.5 mg group (+29.6 m) than in the placebo group (-5.6 m), with an intergroup difference of 35.8 m (95% CI: [20.1; 51.1]). Among the secondary endpoints, PAH severity functional class was unchanged for the majority of patients (75% in the riociguat group and 71% in the placebo group). Nonetheless, it should be noted that the percentage of patients who moved to a less severe functional class (improvement by one class) was slightly higher in the riociguat group with 20.5% of patients versus 14.4% in the placebo group (p=0.003).

In the indication functional class II or III chronic thromboembolic pulmonary hypertension (CTEPH) which is inoperable, or persistent or recurrent after surgical treatment, the application for inclusion is supported by a phase III trial, the CHEST-1 study, which has a similar design to the PATENT-1 study. This study also compared the efficacy of riociguat (1.0-2.5 mg) with placebo, in terms of the distance covered in the 6-minute walk test, in the population indicated and for a treatment period of 16 weeks.
The 261 patients included and treated were aged 59 years on average and had inoperable CTEPH in 72.4% of cases and persistent or recurrent CTEPH after surgery in 27.6% of cases. The majority of patients were in functional class II or III (95%). They had to be naive to all specific treatment for pulmonary hypertension. They were randomised to two groups with a 2:1 randomisation design: a riociguat group (n=173) and a placebo group (n=88).
The change in 6-minute walk distance at 16 weeks was greater in the riociguat group (+38.9 m) than in the placebo group (-5.5 m), with an intergroup difference of 45.7 m (95% CI: [24.7; 66.6]). Among the secondary endpoints, functional class (indicating severity) was unchanged after 16 weeks in 61.8% of patients on riociguat and 78% of patients on placebo, with a greater percentage of patients moving into a less severe functional class in the riociguat group (30.6% versus 14.9% in the placebo group, p=0.003).

These two studies have shown that riociguat is more effective than placebo in both indications, in terms of the change in 6-minute walk distance. However, it is debatable whether this endpoint is relevant in the clinical evaluation of these diseases, and new primary efficacy endpoints, such as time to clinical worsening, should be evaluated.[12,13,14,15] Time to clinical worsening was defined as a

[12] Impens A.J. and al. The 6-minute walk test in scleroderma – how measuring everything measures nothing. Rheumatology 2008; 47: 8-9.
[13] Lewis Rubin and Gérald Simonneau. Perspective on the optimal endpoints for pulmonary arterial hypertension trials. Current Opinion in Pulmonary Medicine 2010; 16: 43-6.
[14] V. McLaughlin and al. end points and clinical trial design in pulmonary arterial hypertension. J. Am. Coll. Cardiol. 2009; 54: 97-107.

secondary endpoint in both these studies, but comparing this time between the riociguat group and the placebo group is not very informative due to the small number of patients who developed clinical worsening during the 12 or 16-week follow-up period (fewer than ten patients per group). As regards patients improving into a less severe functional class than on inclusion, a difference was found versus placebo, particularly for the CTEPH indication.
As regards treatment for PAH, the comparison between riociguat and placebo cannot be used to position this medicine in relation to the other available specific treatments for PAH.
It should be noted that the differences in dyspnoea and quality of life scores have little clinical relevance.

In terms of safety, more than 90% of patients had at least one adverse event, and these were mostly mild to moderate in severity. The most common adverse events related to riociguat were neurological disorders (vertigo, headaches), gastrointestinal disorders (dyspepsia, nausea, vomiting, diarrhoea), peripheral oedema and hypotension. In the two follow-up studies supplied (including patients from the PATENT-1 and CHEST-1 studies respectively), for a treatment duration of between 360 and 390 days, the incidence of serious adverse events linked to riociguat was about 2% to 4% (primarily syncope and hypotension).

[15] N. Galie and al. Clinical worsening in trials of pulmonary arterial hypertension: results and implications. Current Opinion in Pulmonary Medicine 2010; 16: 11-9.

08.4 Planned studies

The PATENT-2 follow-up study for PAH and the CHEST-2 follow-up study for inoperable CTEPH or persistent/recurrent CTEPH after surgery should be completed in 2016.

Three phase IIIb studies are in the enrolment phase:

- The Early Access Study (16097) evaluating the efficacy and safety of riociguat in inoperable CTEPH or persistent/recurrent CTEPH after surgical treatment;
- The RESPITE study (16719) in group 1 PAH in patients with an inadequate response to treatment with phosphodiesterase type 5 inhibitors;
- The EXPERT registry (16657) in both approved indications for riociguat, evaluating its safety over a 4-year follow-up period.

A risk management plan aims to monitor certain safety-related aspects. The risks monitored are:

- important identified risks: hypotension, upper gastrointestinal disorders, worsening of venous occlusive disease, serious haemoptysis;
- important potential risks: bleeding, embryo-fetal toxicity, medication error, renal failure, fractures, off-label use in patients aged < 18 years or treatment of patients with atrial fibrillation or smokers;
- missing information: patients with PAH or CTEPH in functional class IV, or with systolic blood pressure below 95 mmHg or uncontrolled hypertension, or severe hepatic or renal impairment, or aged under 18 years, pregnancy and breast-feeding.

09 THERAPEUTIC USE

The aim of therapeutic management is primarily to improve the patient's survival and quality of life.

Pulmonary arterial hypertension

Since PAH is a severe illness in the short term, regular follow-up is necessary to detect clinical worsening and to enable therapy to be escalated as soon as possible. Assessing the prognosis plays an important role when choosing the initial treatment and assessing the response to treatment.

The therapeutic strategy recommended by the Transparency Committee in these opinions and found in the literature is as follows:

Conventional treatment for PAH combines anticoagulants, diuretics, oxygen therapy and calcium channel blockers.

In patients with class II PAH, endothelin receptor antagonists (ambrisentan, bosentan) or phosphodiesterase inhibitors (sildenafil, tadalafil), which are oral treatments, are recommended.

In patients with class III PAH, endothelin receptor antagonists (bosentan or ambrisentan) and phosphodiesterase inhibitors (sildenafil or tadalafil) can be used as an oral first-line treatment.

As second-line therapy (due to contraindication, poor hepatic tolerance of bosentan or failure of oral treatments), prostacyclin analogues are recommended:

- inhaled iloprost
- intravenous epoprostenol via continuous infusion
- subcutaneous treprostinil. The decision to start treprostinil therapy should take into account the high probability that continuous subcutaneous infusion will have to be maintained in the long term.[16,17,18]

The treatment is evaluated 3 to 4 months after being started. If the patient has met the treatment goals set, treatment is continued together with regular follow-up by the expert centre. If monotherapy fails, a combination of therapies will be discussed. In actual fact, data on the efficacy and role of dual therapy and on the choice of combined drugs are limited.[17]

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

The efficacy of ADEMPAS has been demonstrated versus placebo through an improvement in 6-minute walk distance in the short and medium term, which is similar to the oral proprietary medicinal products indicated in PAH in functional class II to III. It should be noted that ADEMPAS cannot be used in combination with phosphodiesterase type 5 inhibitors, and that where there are risk factors such as recent episodes of serious haemoptysis, riociguat increases the risk of respiratory tract bleeding in these patients who are frequently taking anticoagulants.

Taking account of these points, the ADEMPAS proprietary medicinal products form part of the specific symptomatic treatments available for class II PAH and class III PAH as a first-line therapy, as monotherapy or in combination with endothelin receptor antagonists only.

[16] McLaughlin VV, Archer S, Badesch D et al. ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension. J Am Coll Cardiol 2009; 53: 1574-619.

[17] Haute Autorité de Santé. Réévaluation des traitements de l'hypertension artérielle pulmonaire (HTAP) [Re-assessment of treatments for pulmonary arterial hypertension (PAH)]. Opinion of 5 January 2011.

Chronic thromboembolic pulmonary hypertension

Therapeutic management of CTEPH consists of supportive treatments such as long-term anticoagulants.[18] Pulmonary thromboendarterectomy is the treatment of choice whenever possible as it can restore near-normal cardiorespiratory function.

When this procedure is not possible (distal lesions or comorbidities) or when patients have persistent or recurring symptoms after a thromboendarterectomy, there are currently no alternative treatments. The recommendation to use PAH-specific treatments (endothelin receptor antagonists, phosphodiesterase inhibitors and prostacyclin analogues) in these two cases is based on limited data and these proprietary medicinal products do not have Marketing Authorisation in this indication. In any case, the decision that surgical treatment is impossible should be made through a multidisciplinary consultation in an expert centre before any specific medicinal treatment is prescribed.

The efficacy of the ADEMPAS proprietary medicinal products, indicated in inoperable CTEPH and persistent or recurrent CTEPH after surgery, has been demonstrated versus placebo through an improvement in 6-minute walk distance in the short and medium term, in the absence of any available alternative treatments. From a safety point of view, it should be noted that where there are risk factors such as recent episodes of serious haemoptysis, riociguat increases the risk of respiratory tract bleeding in these patients who are frequently taking anticoagulants.
Taking account of these points, the ADEMPAS proprietary medicinal products have a role in the symptomatic treatment of inoperable CTEPH or persistent or recurrent CTEPH after surgery.

[18] Wilkens H, Lang I, Behr J et al. Chronic thromboembolic pulmonary hypertension (CTEPH): Updated Recommendations of the Cologne Consensus Conference 2011. Int J Cardiol 2011; 154s: 54-60.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual benefit

➢ **Pulmonary arterial hypertension**

◗ Group 1 PAH is a rare, life-threatening lung disease, which is characterised by an increase in pulmonary artery pressure and may lead to right-sided heart failure. Asthenia, progressive exertional dyspnoea, chest pain and loss of consciousness are the most common clinical signs.
◗ These proprietary medicinal products are intended as symptomatic therapy.
◗ In light of the data available, the efficacy/adverse effects ratio is modest.
◗ There are alternative treatments, namely the medicinal products indicated for PAH (administered orally).
◗ The ADEMPAS proprietary medicinal products form part of the specific treatments available for class II and class III PAH as a first-line therapy, as monotherapy or in combination with endothelin receptor antagonists only.

◗ 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 PAH is a public health need that is an established priority (Law of 9 August 2004 on public health policy, Rare Diseases Plan 2011-2014).
In terms of the results from the PATENT-1 study, ADEMPAS has been shown to improve walk distance in comparison with placebo. However, given the lack of long-term comparative efficacy data and of efficacy data comparing riociguat to existing treatments, and since an improvement in quality of life is not relevant, riociguat cannot be established to have any additional impact in comparison with the current management of patients with class II or III PAH in France. In addition, an increased risk of respiratory tract bleeding was observed in these studies.
The applicability of the data to current clinical practice is good, since the populations studied are representative of the population reached.
The ADEMPAS proprietary medicinal products are therefore unable to provide any additional response to the identified public health need.
Consequently, it is not expected that ADEMPAS will have any impact on public health in functional class II or III PAH.

Taking account of these points, the Committee considers that the actual benefit of ADEMPAS is moderate in pulmonary arterial hypertension in functional class II to III in adult patients, as monotherapy or in combination with endothelin receptor antagonists, to improve exercise capacity.

The Committee recommends inclusion on the list of medicines approved for hospital use in the indication "as monotherapy or in combination with endothelin receptor antagonists [...] for the treatment of adult patients with pulmonary arterial hypertension (PAH) with WHO Functional Class (FC) II to III to improve exercise capacity" and at the dosages in the Marketing Authorisation.

➢ **Chronic thromboembolic pulmonary hypertension**

◗ Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare and serious pulmonary complication of venous thromboembolism which can be life-threatening. It is characterised by an increase in pulmonary artery pressure and may lead to right-sided heart failure. Asthenia, progressive exertional dyspnoea, chest pain and loss of consciousness are the most common clinical signs.
◗ These proprietary medicinal products are intended as symptomatic therapy.
◗ In light of the data available, the efficacy/adverse effects ratio is modest.
◗ There is currently no validated treatment alternative.
◗ The ADEMPAS proprietary medicinal products have a role in the symptomatic treatment of inoperable CTEPH or persistent or recurrent CTEPH after surgery in the absence of any alternative treatment.

◗ Public health benefit

Although CTEPH 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 CTEPH is a public health need that is an established priority (Law of 9 August 2004 on public health policy, Rare Diseases Plan 2011-2014).
In terms of the results from the CHEST-1 study, ADEMPAS has been shown to improve walk distance in comparison with placebo, bearing in mind that there is currently no alternative treatment. However, given the lack of long-term comparative efficacy data, and since an improvement in quality of life is not relevant, riociguat cannot be established to have an impact in comparison with the current management of patients with class II or III PAH in France. In addition, an increased risk of respiratory tract bleeding was observed in these studies.
The applicability of the data to current clinical practice is good, since the populations studied are representative of the population reached.
The ADEMPAS proprietary medicinal products therefore provide a partial response to an identified public health need.
Consequently, it is expected that ADEMPAS will have a slight impact on public health in functional class II or III CTEPH that is inoperable, or persistent or recurrent after surgical treatment.

Taking account of these points, the Committee considers that the actual benefit of ADEMPAS is moderate in chronic thromboembolic pulmonary hypertension in functional class II to III which is inoperable, or persistent or recurrent after surgical treatment, to improve exercise capacity.

The Committee recommends inclusion on the list of medicines approved for hospital use in the indication "chronic thromboembolic pulmonary hypertension with functional class II to III which is inoperable, or persistent or recurrent after surgical treatment, to improve exercise capacity" and at the dosages in the Marketing Authorisation.

010.2 Improvement in actual benefit (IAB)

➢ **Pulmonary arterial hypertension**

The ADEMPAS proprietary medicinal products do not provide an improvement in actual benefit (level V, non-existent) in the management of pulmonary arterial hypertension in functional class II to III, in comparison with available specific treatments for pulmonary arterial hypertension.

- **Chronic thromboembolic pulmonary hypertension**

The ADEMPAS proprietary medicinal products provide a minor improvement in actual benefit (level IV) in the management of chronic thromboembolic pulmonary hypertension with functional class II to III which is inoperable, or persistent or recurrent after surgical treatment, in the absence of any alternative treatment.

010.3 Target population

In pulmonary arterial hypertension, the target population for ADEMPAS is patients with functional class II or III PAH.
According to the national pulmonary hypertension registry, 3193 patients in France were reported and treated for PAH in 2011. If we consider that 20% of cases of PAH are class II and 60% are class III, the number of patients concerned would be 2555.[19] According to the 2011 opinion re-assessing PAH medicines, the number of patients with functional class II or III PAH is about 3000 patients.[18]
The target population for this indication is estimated as 3000 patients.

In chronic thromboembolic pulmonary hypertension, the target population for ADEMPAS is patients with functional class II or III CTEPH that is inoperable or persistent/recurrent after surgery.
The prevalence of CTEPH is estimated as 3 per 100,000 inhabitants, which would be 1966 patients in France.[20] According to the international pulmonary hypertension registry, 36% of patients with CTEPH are inoperable, i.e. 708 patients.[21] 16.7% of patients have residual CTEPH, i.e. 214 patients.[21]
In addition, according to expert consensus, the incidence of CTEPH is 300 to 400 new cases a year, i.e. between 108 and 144 inoperable patients and between 50 and 67 patients with residual CTEPH.
The target population for this indication is therefore estimated as 1133 patients.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

Packaging
Appropriate for the prescribing conditions.

[19] Humbert M et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med 2006; 173: 1023-30.
[20] Les Cahiers d'Orphanet, série Maladies Rares. Prévalence des maladies rares: données bibliographiques. November 2013.
[21] Pepke-Zaba J, Delcroix M, Lang I et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation 2011; 124: 1973-81.