The legally binding text is the original French version

TRANSPARENCY COMMITTEE
Opinion
17 September 2014

OPSUMIT 10 mg, film-coated tablet
Blister pack of 30 (CIP: 34009 278 246 1 6)

Applicant: ACTELION

<table>
<thead>
<tr>
<th>INN</th>
<th>macitentan</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC Code (2013)</td>
<td>C02KX04 (Antihypertensives for pulmonary arterial hypertension)</td>
</tr>
<tr>
<td>Reason for the request</td>
<td>Inclusion</td>
</tr>
<tr>
<td>List(s) concerned</td>
<td>Hospital use (French Public Health Code L.5123 2)</td>
</tr>
<tr>
<td>Indications concerned</td>
<td>“OPSUMIT, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III. Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease”.</td>
</tr>
<tr>
<td><strong>Actual Benefit</strong></td>
<td><strong>Moderate</strong></td>
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<tr>
<td><strong>Improvement in Actual Benefit</strong></td>
<td>Given the available clinical data and in the absence of data versus active comparators (other endothelin receptor antagonists or phosphodiesterase type 5 inhibitors), the Committee considers that OPSUMIT (macitentan), 4th agent of the class of endothelin receptor antagonists, does not provide an improvement in actual benefit (IAB V, non-existent) in the therapeutic management strategy of pulmonary arterial hypertension in adult patients of WHO Functional Class II or III.</td>
</tr>
<tr>
<td><strong>Therapeutic Use</strong></td>
<td>First-line treatment</td>
</tr>
<tr>
<td><strong>Recommendations</strong></td>
<td>Inclusion on the list of medicines approved for hospital use is recommended</td>
</tr>
</tbody>
</table>
01 ADMINISTRATIVE AND REGULATORY INFORMATION

<table>
<thead>
<tr>
<th>Marketing Authorisation (procedure)</th>
<th>Initial date (centralised): 20 December 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk minimisation measures will be implemented during marketing of OPSUMIT. They involve the 3 &quot;significant identified risks&quot;: anaemia and reduced level of haemoglobin, hepatotoxicity and teratogenicity (see paragraph 8.2.2)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prescribing and dispensing conditions /special status</th>
<th>List I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orphan medicinal product</td>
<td></td>
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<tr>
<td>Medicine for hospital prescription only. Prescription medicine restricted to specialists in pulmonology, cardiology or internal medicine.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>ATC Classification</th>
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<tbody>
<tr>
<td>2013</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>Cardiovascular system</td>
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<tr>
<td>C02</td>
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<tr>
<td>Antihypertensives</td>
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<tr>
<td>C02K</td>
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<tr>
<td>Other antihypertensives</td>
</tr>
<tr>
<td>C02KX</td>
</tr>
<tr>
<td>Antihypertensives for pulmonary arterial hypertension</td>
</tr>
<tr>
<td>C02KX04</td>
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<tr>
<td>Macitentan</td>
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</tbody>
</table>

02 BACKGROUND

This is a request for inclusion on the list of medicines approved for hospital use for the proprietary medicinal product OPSUMIT, film-coated tablet (macitentan), which obtained Marketing Authorisation on 20 December 2013 accompanied by a RMP and risk minimisation tools intended to inform healthcare professionals and patients about the risks of anaemia, hepatotoxicity and teratogenicity and to list the points to check before prescription.

OPSUMIT (macitentan) is the 4th representative of the class of endothelin receptor antagonists.1

03 THERAPEUTIC INDICATIONS

“OPSUMIT, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III.

Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease”.

04 DOSAGE

See SPC.

05 THERAPEUTIC NEED2,3,4,5,6

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1 The Marketing Authorisation for THELIN (sitaxentan), 3rd representative of the class, was repealed in 2011.
There are five types of pulmonary hypertension. These include pulmonary arterial hypertension (PAH), which can be idiopathic, heritable, drug or toxin-induced, or a complication of certain diseases (connective tissue diseases, congenital heart disease, portal hypertension, HIV infection, etc.).

Pulmonary hypertension is defined as a mean pulmonary artery pressure $\geq 25$ mmHg at rest, measured during right heart catheterisation, and a pulmonary capillary wedge pressure (PCWP) $\leq 15$ mmHg.

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.

In addition to a combination of several specific medicinal products and surgical interventions, therapeutic management of pulmonary arterial hypertension includes general measures (sporting activities where possible, prevention of infections) and associated supportive treatments such as anticoagulants, diuretics and oxygen therapy. The use of specific medicinal products depends 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 in class I to III PAH with arterial vasoreactivity are calcium channel blockers. If there is no pulmonary arterial vasoreactivity or treatment with calcium channel blockers fails, treatment involves:

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

The treatment algorithm is described in table 1. If treatment fails again, a combination of therapies will be discussed.

In cases of severe PAH insufficiently improved by maximum medical treatment, a lung transplant or atrial septostomy pending transplant may be last-resort therapeutic alternatives.³

In theory, the therapeutic needs of most patients with PAH are therefore covered by using these 3 classes of specific PAH treatments, acting on the 3 pathways involved in the pathophysiology of the disease. In addition, the class of endothelin receptor antagonists, of which macitentan (OPSUMIT) is the 4th representative, already have two different active ingredients¹ for which long-term efficacy and safety data are available with a follow-up of longer than 10 years after being released on the market. Nevertheless, this condition remains associated with significant mortality.

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⁵ Les cahiers d’Orphanet, série Maladies rares [Orphanet Report series, Rare Diseases series] Prevalence of rare diseases: literature data. 2013
Table 1. Treatment algorithm according to WHO class for PAH and for a negative vasoreactivity test, based on the best level of evidence.

<table>
<thead>
<tr>
<th>WHO functional class</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I PAH with no functional limitations; normal physical activity does not lead to dyspnoea or excessive fatigue, chest pain or presyncope.</td>
<td>No treatment consensus</td>
</tr>
<tr>
<td>II PAH with slight functional limitations; physical activity leads to dyspnoea or excessive fatigue, chest pain or presyncope. These patients have no symptoms at rest.</td>
<td>Ambrisentan, bosentan, sildenafil, tadalafil. Combination with other medicines from a different class should be discussed.</td>
</tr>
<tr>
<td>III PAH with significant functional limitations; even light physical activity leads to dyspnoea or excessive fatigue, chest pain or presyncope. These patients have no symptoms at rest.</td>
<td>Ambrisentan, bosentan, sildenafil, tadalafil, As second-line treatment: IV epoprostenol, inhaled iloprost, treprostinil. Combination with other medicines from a different class should be discussed.</td>
</tr>
<tr>
<td>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.</td>
<td>IV epoprostenol combined with the other treatments above.</td>
</tr>
</tbody>
</table>

A response to treatment for pulmonary hypertension is indicated by an increase in the distance walked during the 6-minute walk test (> 380 or 440 m), a return to functional class I or II, normalisation of haemodynamic and ultrasound parameters, BNP levels, and maximum oxygen consumption > 15 ml/min/kg.⁷

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

The relevant comparators of OPSUMIT are the specific medicinal products for PAH, indicated in the treatment of PAH of functional classes II and III administered as first-line treatment in addition to supportive treatments such as anticoagulants, diuretics and oxygen therapy, namely:

- endothelin receptor antagonists
- phosphodiesterase type 5 inhibitors.

<table>
<thead>
<tr>
<th>NAME (INN) Company</th>
<th>Indication</th>
<th>Date of TC opinion</th>
<th>AB</th>
<th>IAB (Wording)</th>
<th>Reimbursement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endothelin receptor antagonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRACLEER (bosentan) Actelion Pharmaceuticals France</td>
<td>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 associated with 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) WHO functional class II.</td>
<td>05/01/2011 (PAH re-assessment)</td>
<td>Moderate</td>
<td>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.</td>
<td>Yes (hospital use)</td>
</tr>
<tr>
<td>VOLIBRIS (ambrisentan) GlaxoSmithKline</td>
<td>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.</td>
<td>05/01/2011 (PAH re-assessment)</td>
<td>Moderate</td>
<td>The Transparency Committee considers that the VOLIBRIS proprietary medicinal products provide a minor improvement in actual benefit (IAB IV) in the treatment of idiopathic PAH or PAH associated with systemic collagen tissue disease in patients in functional class II or III.</td>
<td>Yes (hospital use)</td>
</tr>
</tbody>
</table>

Phosphodiesterase inhibitors
<table>
<thead>
<tr>
<th>NAME (INN) Company</th>
<th>Indication</th>
<th>Date of TC opinion</th>
<th>AB</th>
<th>IAB (Wording)</th>
<th>Reimbursement</th>
</tr>
</thead>
<tbody>
<tr>
<td>REVATIO (sildenafil) Pfizer</td>
<td>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.</td>
<td>05/01/2011 (PAH re-assessment)</td>
<td>Moderate</td>
<td>The Transparency Committee considers that the proprietary medicinal product REVATIO provides a minor improvement in actual benefit (IAB IV) in the treatment of idiopathic PAH or PAH associated with systemic collagen tissue disease in patients in functional class II or III.</td>
<td>Yes (hospital use)</td>
</tr>
</tbody>
</table>
|                    | Treatment of pulmonary arterial hypertension in children and adolescents aged from 1 year to 17 years old. 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 from sildenafil tablets is part of current clinical practice, and this use is justified by the few treatment alternatives suitable for use in pediatrics. 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 offer any improvement in actual benefit (IAB V) in the management of pulmonary arterial hypertension in children and adolescents aged from 1 to 17 years suffering from PAH;  
 - REVATIO 10 mg/ml, powder for oral suspension, is an addition to the range which is useful for the treatment of PAH in children and adolescents aged from 1 to 17 years suffering from PAH and in adults unable to swallow film-coated tablets. | Yes (hospital use) |
<p>| ADCIRCA (tadalafil) Lilly France | ADCIRCA is indicated in adults for the treatment of 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 proprietary medicinal product ADCIRCA provides a minor improvement in actual benefit (IAB 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 | 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 (IAB IV) in the treatment of idiopathic pulmonary arterial hypertension in patients in functional class III. | Yes (hospital use) |</p>
<table>
<thead>
<tr>
<th>NAME (INN) Company</th>
<th>Indication</th>
<th>Date of TC opinion</th>
<th>AB</th>
<th>IAB (Wording)</th>
<th>Reimbursement</th>
</tr>
</thead>
</table>
| FLOLAN and its generics (epoprostenol) GlaxoSmithKline | FLOLAN is indicated for long-term treatment, by means of continuous infusion, of pulmonary arterial hypertension (PAH):  - idiopathic pulmonary arterial hypertension  - familial or sporadic,  - pulmonary arterial hypertension associated with systemic collagen disease,  
In patients in clinical functional 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 (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. | Yes (hospital use) |
| 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 (IAB IV) in the treatment of idiopathic pulmonary arterial hypertension in patients in functional class III. | Yes (hospital use) |

### 06.2 Other health technologies

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

#### Conclusion

The clinically relevant comparators are the other endothelin receptor antagonists and phosphodiesterase type 5 inhibitors.
<table>
<thead>
<tr>
<th>Country</th>
<th>REIMBURSEMENT</th>
<th>Population(s) That of the Marketing Authorisation or restricted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>Yes</td>
<td>100% reimbursement Dispensed by the hospital and local pharmacy</td>
</tr>
<tr>
<td>Great Britain</td>
<td>Under assessment</td>
<td>Dispensed by the hospital, local pharmacy and treatment taken to the patient's home</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Under assessment</td>
<td>Dispensed by the hospital and local pharmacy</td>
</tr>
</tbody>
</table>

08 ANALYSIS OF AVAILABLE DATA

Assessment of the efficacy and safety of OPSUMIT in PAH is based on:
- A phase II study (AC-055-201) performed on 379 patients with essential hypertension, the objective of which was to determine the optimal dosage of macitentan to be tested in the pivotal study (phase III) which will not be discussed in this opinion.
- A phase III study (AC-055-302 SERAPHIN)\(^8\) the objective of which was to determine the efficacy of macitentan compared with placebo in terms of morbidity and mortality in 742 patients with PAH.

The company also reported a phase II study (MUSIC - AC - 055B201) which evaluated the efficacy and safety of macitentan compared with placebo on lung function test parameters (forced vital capacity - FVC) in 178 patients with pulmonary fibrosis. This study concluded that macitentan had no effect on the change in FVC and that there was no difference compared with placebo; it will not be discussed in this opinion insofar as this indication has not been selected in the OPSUMIT MA.

08.1 Efficacy

Method: phase III, randomised, double-blind, comparative study of macitentan 3 and 10 mg versus placebo (1:1:1) evaluating efficacy in terms of morbidity and mortality (based on the occurrence of the first event from those included in the composite endpoint) in 742 patients with symptomatic PAH in functional class II to IV, with a mean follow-up of 96 weeks (median follow-up of 115 weeks).

Inclusion criteria: Patients aged 12 years and over with symptomatic PAH in functional classes II to IV:
- confirmed by haemodynamic diagnosis: pulmonary arterial pressure ≥ 25 mmHg, PCWP or end-diastolic pressure of the left ventricle ≤ 15 mmHg, pulmonary vascular resistance at rest 320 dyn.sec/cm\(^5\).

\(^8\) Pulido et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. NEJM 2013; 369: 809-18.
- with PAH:
  - idiopathic,
  - heritable,
  - associated with connective tissue disease, simple congenital heart disease (left-right shunt operated on more than one year ago), HIV infection or drug or toxin-induced,
- distance walked in 6 minutes (6MWT) ≥ 50 m.

Treatment:
- Macitentan 3 mg, n=250,
- Macitentan 10 mg, n=242,
- Placebo, n=250.

Primary efficacy endpoints: occurrence of the first morbidity-mortality event from the following events (combined endpoint):
- Death or adverse effects resulting in death during the 4 weeks following treatment discontinuation,
- Atrial septostomy or hospitalisation for atrial septostomy,
- Lung transplant or hospitalisation for lung transplant,
- Initiation of IV or subcutaneous [SC] prostanoid treatment (epoprostenol, treprostinil) or hospitalisation for initiation of these treatments,
- worsening of the PAH defined by the occurrence of 3 of the following events:
  - reduction by at least 15% of the 6MWT,
  - worsening of the symptoms of PAH including at least one of the following elements: worsening of the PAH functional class or lack of improvement, onset of worsening of signs of right-sided heart failure not responding to optimised diuretic treatment,
  - necessity for further PAH treatment: oral prostanoids or phosphodiesterase inhibitors, endothelin receptor antagonists after discontinuation of the study treatments, IV diuretics.

This combined endpoint chosen as the primary endpoint is based on very heterogeneous endpoints with different relevance in terms of morbidity-mortality evaluation.

Secondary endpoints, in particular: change in the 6MWT after 6 months, time until death or hospitalisation for PAH, death from any cause...

Statistical analysis:
Given the multiple tests between the 2 doses of macitentan and the placebo, Bonferroni correction was integrated due to the α risk inflation.
To conclude, the significance level was fixed at 0.025 for the primary endpoint and 0.05 for the secondary endpoints. Nevertheless, to conclude, the company fixed a higher significance level with an alpha risk of 0.01.

RESULTS: see table 1
The patients’ characteristics at inclusion were generally comparable.
Distribution depending on the functional classes was as follows:
- class I: a single patient in the macitentan 10 mg group (0.4%)
- class II: 138/248 (55.6%) in the macitentan 3 mg group, 120/242 (49.6%) in the macitentan 10 mg group and 129/249 (51.8%) in the placebo group,
- class III: 105/248 (42.3%), 116/242 (47.9%) and 116/249 (46.6%).
It should be noted that around 2% of patients included were in functional class IV: 5 patients in the macitentan 3 mg group (2.0%), 5 patients in the macitentan 10 mg group (2.1%) and 4 patients in the placebo group (1.6%).

The mean pulmonary artery pressure at inclusion was 55.1 mmHg (SD 16.74), 53.5 mmHg (SD 17.63) and 53.1 mmHg (SD 18.13).
The mean 6MWT at inclusion was 364.1 m (SD 95.52), 362.6 m (SD 93.21) and 352.4 m (SD 110.62).

PAH - specific concomitant treatments were used in 63.7% of patients and distributed homogeneously between the treatment groups:
- sildenafil: 57.6% of patients,
- iloprost: 3.5%
- vardenafil: 2.8%
- beraprost: 2%
- tadalafil: 0.9%
- treprostinil: 0.1%

Table 1: Results

<table>
<thead>
<tr>
<th></th>
<th>Macitentan 3 mg N=250</th>
<th>Macitentan 10 mg N=242</th>
<th>Placebo n=250</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of events (%)</td>
<td>95 (38%)</td>
<td>76 (31.4%)</td>
<td>116 (46.4%)</td>
</tr>
<tr>
<td>HR [97.5% CI]</td>
<td>0.704 [0.513; 0.960]</td>
<td>0.547 [0.392; 0.762]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>p (vs. placebo)</td>
<td>0.0108</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td><strong>Components of the primary endpoint:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Death</td>
<td>21 (8.4%)</td>
<td>16 (6.6%)</td>
<td>17 (6.8%)</td>
</tr>
<tr>
<td>- Atrial septostomy</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- Transplantation</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- Initiation of a prostanoid (IV or subcutaneous)</td>
<td>1 (0.4%)</td>
<td>1 (0.4%)</td>
<td>6 (2.4%)</td>
</tr>
<tr>
<td>- Worsening of PAH</td>
<td>72 (28.8%)</td>
<td>59 (24.4%)</td>
<td>93 (37.2%)</td>
</tr>
<tr>
<td><strong>Other secondary endpoints:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 6MWT at 6 months (m), Difference [97.5% CI]</td>
<td>7.4</td>
<td>12.5</td>
<td>-9.4</td>
</tr>
<tr>
<td>p (vs. placebo)</td>
<td>16.8 [-2.7; 36.4]</td>
<td>22 [3.2; 40.8]</td>
<td>0.0122</td>
</tr>
<tr>
<td><strong>Time until death or hospitalisation for PAH,</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR [97.5% CI]</td>
<td>0.669 [0.462; 0.970]</td>
<td>0.500 [0.335; 0.747]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>p (vs. placebo)</td>
<td>0.0146 (NS)</td>
<td>0.0078 (NS)</td>
<td></td>
</tr>
<tr>
<td><strong>Death from any cause (n)</strong></td>
<td>210.971 [0.477; 1.976]</td>
<td>140.638 [0.287; 1.418]</td>
<td>19</td>
</tr>
<tr>
<td>p (vs. placebo)</td>
<td>0.9249 (NS)</td>
<td>0.2037 (NS)</td>
<td></td>
</tr>
</tbody>
</table>

A significant reduction in terms of occurrence of the first morbidity-mortality event (combined endpoint associating deaths or atrial septostomy or hospitalisation for atrial septostomy or lung transplant or initiation of IV or SC prostanoid (epoprostenol, treprostinil) or hospitalisation for initiation of these treatments or worsening of PAH) was observed in the macitentan 10 mg group compared with placebo: 76 events (31.4%) versus 113 (46.4%), HR 0.547 97.5% CI [0.392; 0.762], p<0.0001.

This result is mainly based on the reduction of PAH worsening events: 59 (24.4%) events versus 93 (37.2%). Statistical analysis of each of the endpoints constituting the combined endpoint was not planned in the protocol; this analysis is only available for worsening of PAH and initiation of a prostanoid).

No difference was observed in terms of mortality as a first event between the macitentan 10 mg arm and the placebo: 16 deaths (6.6%) versus 17 (6.8%). Similarly, no significant difference was
observed for the number of deaths from any cause until the end of the study with 35 deaths in the macitentan 10 mg group and 44 in the placebo group (HR = 0.77; 97.5% CI [0.46 to 1.28]).

In terms of occurrence of the first morbidity-mortality event, a reduction was observed in the macitentan 3 mg group compared with the placebo: 95 events (38%) versus 116 (46.4%), HR 0.704 97.5% CI [0.516; 0.960], p=0.0109, results not conclusive taking into account the high threshold fixed by the company.

No difference was observed in terms of mortality between macitentan 3 mg and the placebo (21 patients (8.4%) versus 17 patients (6.4%)). This dosage was not selected in the MA insofar as the results for the primary efficacy endpoint did not reach the significance level required for registration, namely p<0.01 (results obtained p<0.025).

08.2 Adverse effects

8.2.1 Data from clinical studies

In the SERAPHIN study, adverse effects were observed in 240/250 patients (96.0%) in the macitentan 3 mg group, 229/242 patients (94.6%) in the macitentan 10 mg group and 240/249 patients (96.4%) in the placebo group. The most common adverse effects (>14%) were:

- PAH: 30.0% versus 21.9% versus 34.9%
- Upper respiratory tract infection: 20.0% versus 15.3% versus 13.3%
- Peripheral oedema: 16.0% versus 18.2% versus 18.1%
- Nasopharyngitis: 14.8% versus 14.0% versus 10.4%
- Right-sided heart failure: 14.8% versus 13.2% versus 22.5%

Concerning hepatic effects (adverse effects observed with the entire class of endothelin receptor antagonists), hepatic damage was observed in 23 patients (9.2%) in the macitentan 3 mg group, 21 patients in the macitentan 10 mg group (8.7%) and 36 patients (14.5%) in the placebo group:

- Macitentan 3 mg versus placebo: RR 0.636 [0.389; 1.042]
- Macitentan 10 mg versus placebo, RR 0.600 [0.361; 0.998].

AST/ALT elevations, 3 times higher than normal, were observed in 9 patients (3.6%), 8 patients (3.4%) and 11 patients (4.5%) respectively.

AST/ALT elevations, 8 times higher than normal: 4 patients (1.6%), 5 patients (2.1%) and 1 patient (0.4%) respectively.

8.2.2 RMP data

The OPSUMIT Marketing Authorisation is accompanied by a RMP in which the following risks are identified:

- **significant risks identified**: anaemia, reduced level of haemoglobin, hepatotoxicity and teratogenicity.
- **Potential significant risks**: symptomatic hypotension, thrombocytopenia, leucopenia, menstrual disorders (haemorrhages), ovarian cysts, pulmonary oedema associated with veno-occlusive disease, testicular disorders and male fertility disorders, off-label use (particularly paediatric).
- **Missing information**: paediatric population, patients aged over 75 years, patients with moderate to severe hepatic impairment, patients with severe or dialysed renal impairment.

Risk minimisation measures in addition to those in the SPC have been implemented concerning the significant risks identified.

8.2.3 SPC data
According to the SPC "The most commonly reported adverse drug reactions are nasopharyngitis (14.0%), headache (13.6%) and anaemia (13.2%). The majority of adverse reactions are mild to moderate in intensity."

Concerning hepatic function, the SPC specifies that:
"Elevations of liver aminotransferases (AST, ALT) have been associated with PAH and with endothelin receptor antagonists (ERAs). OPSUMIT is not to be initiated in patients with severe hepatic impairment or elevated aminotransferases (> 3 × ULN) and is not recommended in patients with moderate hepatic impairment. Liver enzyme tests should be obtained prior to initiation of OPSUMIT.

Patients should be monitored for signs of hepatic injury and monthly monitoring of ALT and AST is recommended. If sustained, unexplained, clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin > 2 × ULN, or by clinical symptoms of liver injury (e.g., jaundice), OPSUMIT treatment should be discontinued.

Reinitiation of OPSUMIT may be considered following the return of hepatic enzyme levels to within the normal range in patients who have not experienced clinical symptoms of liver injury. The advice of a hepatologist is recommended."

08.3 Summary and discussion

Evaluation of the efficacy and safety of OPSUMIT in PAH is mainly based on a randomised, double-blind, phase III study (AC-055-302 SERAPHIN) the objective of which was to determine the efficacy of macitentan compared with placebo in terms of morbidity and mortality in 742 patients with PAH.

Main efficacy results:
In this study, 742 patients with symptomatic PAH in functional class II to IV were randomised (1:1:1) in the macitentan 3 mg, 10 mg and placebo groups. The efficacy of macitentan was evaluated in terms of morbidity-mortality (clinical benefit with significant reduction in terms of occurrence of the first morbidity-mortality event). A significant reduction of this combined endpoint was observed in the macitentan 10 mg group compared with placebo: 76 events (31.4%) versus 116 (46.4%), HR 0.547 97.5% CI [0.392; 0.762], p<0.0001.

This result is mainly based on the reduction of PAH worsening events and for which 59 (24.4%) events versus 93 (37.2%) were observed. No difference was observed in terms of mortality as a first event between the macitentan 10 mg arm and the placebo: 16 deaths (6.6%) versus 17 (6.8%).

Concerning 6MWT (secondary endpoint), the overall observed improvement was low and quantitatively less than that observed in short-term studies performed with other available treatments.

It should be noted that around 2% of patients included were in functional class IV: 4 patients in the placebo group (1.6%), 5 patients in the macitentan 3 mg group (2.0%) and 5 patients in the macitentan 10 mg group (2.1%). Given the low number of patients included in this functional class, this was not selected in the MA indication.

This macitentan 3 mg dosage, for which inconclusive results were obtained for the primary endpoint (p<0.025) was not selected in the MA insofar as the results for the primary efficacy endpoint did not reach the significance level required for registration, namely p<0.01. In addition, no difference was observed in terms of mortality between macitentan 3 mg and the placebo (21 patients (8.4%) versus 17 patients (6.4%)).

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9 Combined endpoint associating deaths or atrial septostomy or hospitalisation for atrial septostomy or lung transplant or initiation of IV or SC prostanoid (epoprostenol, treprostinil) or hospitalisation for initiation of these treatments or worsening of PAH
Main safety results:
In the SERAPHIN study, the main adverse effects observed were: PAH, upper respiratory tract infections, peripheral oedema, nasopharyngitis and right-sided heart failure.

According to the SPC "The most commonly reported adverse drug reactions are nasopharyngitis (14.0%), headache (13.6%) and anaemia. The majority of adverse reactions are mild to moderate in intensity."

Concerning hepatic function, the SPC advises monitoring at treatment initiation and monthly throughout treatment.

The MA is accompanied by a RMP and risk minimisation measures (in addition to those in the SPC) in particular concerning the following adverse effects: anaemia, reduced levels of haemoglobin, hepatotoxicity and teratogenicity.

This RMP also covers missing information in: the paediatric population, patients aged over 75 years, patients with moderate to severe hepatic impairment, patients with renal impairment.

Discussion:
The available data are based on a study of morbidity-mortality versus placebo which concluded in favour of macitentan 10 mg on a combined endpoint combining elements of different weights. However, this result is mainly based on the reduction of PAH worsening events. No difference in terms of morbidity was observed in the combined primary efficacy endpoint.

The absence of comparative data, in particular versus clinically relevant comparators (other endothelin antagonists, phosphodiesterase type 5 inhibitors), poses a problem regarding the positioning of this product in the management strategy compared with the existing treatments and does not enable assessment of the contribution of this medicinal product compared with others.

08.4 Planned studies
The company has indicated that no study has been requested by a health authority as part of a RMP.

The company also reported future developments and in particular the following studies:
- Long-term extension of the pivotal study of registration of macitentan in PAH (SERAPHIN OL)
- Validation of a quality of life questionnaire specific to PAH (PAH-SYMPACT) according to the FDA criteria in 2 phase IIIb studies (SYMPHONY and ORCHESTRA).
- The extension of indication in Eisenmenger syndrome (MAESTRO) - the most advanced form of PAH associated with congenital heart diseases.
- The Paediatric Investigation Plan (3 studies), in PAH and persistent pulmonary arterial hypertension in the newborn. This plan has been approved by the Paediatric Committee of the EMA.
- Japanese population suffering from PAH.
- Investigation of the effect of macitentan in other forms of PAH, outside of group I (phase II studies).

The development of a dispersible tablet is also ongoing, in particular for use as part of paediatric studies in children aged less than 7 years. Its availability is planned for June 2015.
The aim of therapeutic management is primarily to improve the patient’s survival and quality of life. Since PAH is a severe disease over the short term, regular follow-up is necessary for early detection of clinical exacerbation and also to enable therapy to be increased 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 treatment (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 must take account of the high probability of it being necessary to persist with continuous subcutaneous infusion in the long term.14

The treatment is assessed 3 to 4 months after its initiation. If the patient has achieved the treatment targets, it is continued, together with regular follow-up by the reference centre and expert centre.

If monotherapy fails, a combination of therapies will be discussed. In fact, data on the efficacy and role of dual therapy and on the choice of combined substances are limited.15
A lung or heart-lung transplant is a last-resort treatment. It is generally considered in patients who have not improved after 3 months of medical treatment.

The importance of regular follow-up for these patients should be emphasised, in order to monitor the efficacy of treatment and check for exacerbation on treatment.

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**Therapeutic use of OPSUMIT:**
The efficacy of macitentan 10 mg (OPSUMIT) has been demonstrated versus placebo for a combined morbidity-mortality endpoint, associating elements of different weight, based only on the reduction of PAH worsening events. No difference was observed in terms of all causes of mortality until the end of the study. In this context, in patients with PAH of functional class II to III, macitentan (OPSUMIT), as monotherapy or in combined treatment, represents a new alternative to the currently available first-line symptomatic treatments (other endothelin receptor antagonists and phosphodiesterase inhibitors).
In view of all the above information, and following the debate and vote, the Committee’s opinion is as follows:

010.1 Actual benefit

- PAH is a rare, life-threatening lung disease, which is characterised by an increase in pulmonary artery pressure and by right-sided heart failure. Asthenia, progressive exertional dyspnoea, chest pain and loss of consciousness are the most common clinical signs.

- OPSUMIT is intended as symptomatic treatment.

- There are treatment alternatives, in particular other endothelin receptor antagonists as well as phosphodiesterase type 5 inhibitors.

- In theory, the therapeutic needs of most patients with PAH are covered by using these 3 classes of specific PAH symptomatic treatments, acting on the 3 pathways involved in the pathophysiology of the disease. In addition, the class of endothelin receptor antagonists, of which macitentan (OPSUMIT) is the 4th representative, already have two different active ingredients for which long-term efficacy and safety data are available with a follow-up of longer than 10 years after being released on the market.

The efficacy of macitentan 10 mg (OPSUMIT) has been demonstrated versus placebo for a combined morbidity-mortality endpoint, associating sub-criteria of different clinical relevance, based mainly on the reduction of PAH worsening events. There was no observed difference in terms of mortality whether as a first event of the primary combined efficacy endpoint or in terms of all causes of mortality until the end of the study. In the absence of a comparative study versus an active comparator, the contribution of macitentan compared with its comparators, and in particular the other endothelin receptor antagonists, cannot be quantified.

Effects on hepatic function and haemoglobin have been observed in studies; in the absence of comparative data versus other endothelin receptor antagonists, contribution of this new substance in terms of safety cannot be established.

Therefore, as with the other endothelin receptor antagonists, the efficacy/adverse effects ratio of OPSUMIT is moderate.

- As with the other endothelin receptor antagonists, OPSUMIT (macitentan) is a first-line treatment for class II and III PAH.

- **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 established priority (Law of 9 August 2004 on public health policy, Rare Diseases Plan).

  In light of the results of the SERAPHIN study, OPSUMIT has demonstrated a significant reduction of morbidity (disease progression) at 3 years compared with placebo but no significant difference was observed in terms of mortality.

  However, in the absence of a superiority study versus an active comparator, the additional impact of macitentan compared with the current management of patients with class II or III PAH in France cannot be established.
A statistically significant improvement, although not clinically relevant (<5 points) in quality of life for the physical and mental components of the SF-36 generic questionnaire, was demonstrated at 6 and 12 months versus placebo. In addition, no increased risk of hepatic side effects (side effects of the class of endothelin receptor antagonists) has been reported versus placebo. An impact on the organisation of care by reducing hospitalisations could be assumed, although, this impact cannot be determined from the results of this trial versus placebo. The transferability of study data from the SERAPHIN trial to current clinical practice is not assured. The proprietary medicinal product OPSUMIT is therefore unable to provide any additional response to the identified public health need. Consequently, based on the currently available data, OPSUMIT is not expected to impact public health in its indication.

Taking account of these points, the Committee considers that the actual benefit of OPSUMIT as monotherapy or in combination, for the long-term treatment of pulmonary arterial hypertension in adult patients of WHO Functional Class II to III, is moderate.

The Committee recommends inclusion on the list of medicines approved for hospital use in the indication and at the dosages in the Marketing Authorisation.

Proposed reimbursement rate: 30%

010.2 Improvement in actual benefit (IAB)

Given the available clinical data and in the absence of data versus active comparators (other endothelin receptor antagonists or phosphodiesterase type 5 inhibitors), the Committee considers that OPSUMIT (macitentan), 4th representative of the class of endothelin receptor antagonists, does not provide an improvement in actual benefit (IAB V, non-existent) in the therapeutic management strategy of pulmonary arterial hypertension in adult patients of WHO Functional Class II or III.

010.3 Target population

The target population for OPSUMIT corresponds to patients with pulmonary arterial hypertension of functional class II or III. According to the national pulmonary hypertension registry, 3,193 patients in France were reported and treated for PAH in 2011. If we consider that 20% of PAH cases are class II and 60% are class III, the number of patients concerned would be 2,555. According to the 2011 opinion reassessing PAH medicines, the number of patients with functional class II or III PAH is about 3,000 patients. On the basis of these data, the target population for OPSUMIT can be estimated at 3,000 patients.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

Packaging
Appropriate for the prescribing conditions according to the indication, dosage and treatment duration.