HAUTE AUTORITÉ DE SANTÉ

CARDIOLOGY
Focus
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BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

OPSUMIT (macitentan), endothelin receptor antagonist

No clinical benefit demonstrated in patients with class II or III functional status of pulmonary arterial hypertension by comparison with the comparators.

- OPSUMIT has Marketing Authorisation, in monotherapy or in combination, for the long-term treatment of adults with class II or III functional status of pulmonary arterial hypertension (PAH). Its efficacy has been demonstrated in patients with idiopathic and heritable PAH or PAH associated with connective tissue disorders or corrected simple congenital heart disease.
- A study against placebo has shown a reduction in the worsening of PAH, but no reduction in mortality.
- There are no studies versus the other active comparators: endothelin receptor antagonists or phosphodiesterase type 5 inhibitors.

Therapeutic use

- 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 combined 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 and prescribed, where applicable, in combination:
  - 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.
- The treatment is assessed 3 to 4 months after its initiation. If the patient has achieved the set 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 of dual therapy are limited; the place of this combination and the choice of substances for combination have yet to be clarified.
- 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.
- **Role of the medicinal product in the therapeutic strategy**
  In patients with PAH of functional class II to III, 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 type 5 inhibitors).

Clinical data

- The efficacy of macitentan has been evaluated in one study in which 742 patients with class II to IV functional status of symptomatic PAH were randomised (1:1:1) to the groups macitentan 3 mg (not covered by the Marketing Authorisation), 10 mg and placebo. A significant reduction of morbidity and mortality (combined endpoint covering deaths, atrial septostomy or hospitalisation for atrial septostomy, lung transplant or hospitalisation for lung transplant, initiation of prostanoid treatment or worsening of PAH) 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 between the macitentan 10 mg arm and placebo was observed in terms of mortality as a first event: 16 deaths (6.6%) versus 17 (6.8%).

- 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.
- The methodological weaknesses of the retrospective, purely exploratory, indirect comparisons versus TRACLEER mean that they have no evidential value and do not allow an estimate to be made of the benefit of OPSUMIT compared with TRACLEER.

Special prescribing conditions

- Hospital prescription restricted to specialists in cardiology, internal medicine or pulmonology.
- Medicinal product requiring special monitoring during treatment.

Benefit of the medicinal product

- The actual benefit* of OPSUMIT (macitentan) is moderate.
- OPSUMIT does not provide clinical added value (CAV V) in the therapeutic strategy for management of patients with pulmonary arterial hypertension in WHO functional class II or III.
- Recommends continued inclusion on the list of reimbursable products for hospital use.

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This document was created on the basis of the Transparency Committee Opinion of 02 December 2015 (CT-14497) and is available at **www.has-sante.fr**

[i] * The actual benefit (AB) of a proprietary medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the AB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means "no clinical added value".