HAUTE AUTORITÉ DE SANTÉ

CARDIOLOGY
New medicinal product
October 2017

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

UPTRAVI (selexipag), antithrombotic

Low clinical benefit in the treatment of pulmonary arterial hypertension (PAH) in functional class III, in triple therapy, but no clinical benefit demonstrated in the management of this disease

Insufficient clinical benefit to justify its inclusion on the list of reimbursable products for the treatment of PAH in WHO functional class II or III in monotherapy or dual therapy

Main points

- UPTRAVI has a Marketing Authorisation in the treatment of pulmonary arterial hypertension (PAH) in WHO functional class II-III, in combination, in patients inadequately controlled by an endothelin receptor antagonist (ERA) and/or by a phosphodiesterase type 5 (PDE5) inhibitor, and in monotherapy in patients who are not candidate for these therapies.
- Its efficacy, alone or in combination with an ERA and/or a PDE5 inhibitor, has been demonstrated only compared with placebo, after a median duration of 15 to 17 months, primarily on the reduction of worsening of PAH. No difference was observed on mortality compared with placebo.
- It is a PAH medicine that uses the prostacyclin pathway. Its use is required in PAH from functional class III and only in patients inadequately controlled by a dual therapy with ERA/PDE5 inhibitor, as part of a triple therapy with these two substances.

Therapeutic use

- Conventional treatment for PAH combines anticoagulants, diuretics, oxygen therapy and calcium channel blockers.
- ERAs or PDE5 inhibitors are recommended in monotherapy for PAH of functional class II or III. A combination of these specific treatments in sequential administration is recommended in case of failure of monotherapy. The use of a combination from the outset in functional class II or III may be considered. When the PAH is not adequately controlled by dual therapy, the addition of medicinal products acting on the prostacyclin pathway to an ERA and a PDE5 inhibitor pathway in combination are considered.
- **Role of the medicinal product in the therapeutic strategy**
  UPTRAVI can only be prescribed in patients with PAH in functional class III who are inadequately controlled by a dual therapy with ERA and a PDE5 inhibitor, as part of a triple therapy with these twodrugs . In these patients, UPTRAVI must be used only in second-line intention, in patients who cannot receive an injectable prostacyclin analogue.

Clinical data

- In one study, 1156 patients with symptomatic PAH in functional class II and III were randomised into the selexipag (maximum tolerated individual dose) and placebo groups, alone or in combination with an ERA and/or a PDE5 inhibitor. The efficacy of selexipag was evaluated on a composite endpoint (clinical benefit as the time to first morbidity or mortality event). The risk of occurrence of the first morbidity or mortality event was reduced compared to placebo (HR=0.61; 99% CI: [0.46;0.81], p<0.0001). The most commonly reported first event was hospitalisation due to worsening of PAH (clinical signs of right-sided heart failure), followed by progression of PAH.

A difference of 12 meters in the median walking distance at 26 weeks (secondary endpoint) was found compared to placebo in the 6-minute walk test (p=0.003). There was no difference between the groups in all-cause mortality at the end of the study.

- The adverse events primarily reported were related to the prostacyclin pathway: headaches, gastrointestinal disorders, jaw pain and pain in the extremities. Other adverse events reported included : hyperthyroidism, arterial hypotension requiring monitoring and/or contraindications

Special prescribing conditions

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

Benefit of the medicinal product

- The actual benefit* of UPTRAVI is:
  - low in the treatment of PAH in WHO functional class III, in triple therapy with an ERA and a PDE5 inhibitor, in patients inadequately controlled by these two drugs in combination,
  - insufficient to justify reimbursement by National Health Insurance:
    - in the treatment of PAH in WHO functional class II,
    - in the treatment of PAH in WHO functional class III, in monotherapy or dual therapy with an ERA and a PDE5 inhibitor, in patients adequately controlled by these substances.

- UPTRAVI does not provide any clinical added value** (CAV V) in the therapeutic strategy for management of treatment of functional class III pulmonary arterial hypertension.
- Recommends inclusion on the list of reimbursable products for hospital use only in the treatment of PAH in WHO functional class III, only in triple therapy with an endothelin receptor antagonist (ERA) and by a phosphodiesterase type 5 (PDE5) inhibitor, in patients inadequately controlled by these two drugs in combination.

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This document was created on the basis of the Transparency Committee Opinion of 25 October 2017 (CT-16185) and is available at **www.has-sante.fr**

* 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”.