BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

ADEMPAS (riociguat), antihypertensive for pulmonary arterial hypertension

No clinical benefit demonstrated in functional class II or III pulmonary arterial hypertension when compared with available therapies.
Minor improvement in the treatment of class II or III chronic thromboembolic pulmonary hypertension that is inoperable or persistent/recurrent following surgical treatment.

Main points

- ADEMPAS has Marketing Authorisation in the treatment of:
  - WHO functional class II or III pulmonary arterial hypertension (PAH), as monotherapy or in combination with an endothelin receptor antagonist
  - WHO functional class II or III chronic thromboembolic pulmonary hypertension that is inoperable or persistent/recurrent following surgical treatment.
- In both indications, its efficacy has been demonstrated relative to placebo by a moderate improvement in the walking distance, but there are no data relating to its efficacy in relation to morbidity and mortality.
- It cannot be used in combination with phosphodiesterase type 5 inhibitors.
- The risk of respiratory tract bleeding is increased by riociguat among patients who are frequently taking anticoagulants in the presence of risk factors such as recent episodes of serious haemoptysis.

Therapeutic use

- **In pulmonary arterial hypertension (class II or III):**
  - In newly diagnosed patients, the initiation of disease-modifying treatment is discussed.
  - In patients with class II PAH, the following oral therapies are used: endothelin receptor antagonists (ambrisentan, bosentan) or phosphodiesterase inhibitors (sildenafil, tadalafil). If monotherapy fails, a combination of therapies is considered.
  - 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. They are sometimes combined.
  - As second-line therapy (due to contraindication, hepatic intolerance of bosentan or failure of oral treatments), prostacyclin analogues are recommended:
    - inhaled iloprost,
    - intravenous epoprostenol as a continuous infusion,
    - subcutaneous treprostinil. The decision to embark on treprostinil therapy must take account of the high probability of it being necessary to persist with continuous subcutaneous infusion in the long term.
  - The overall management of PAH combines, in particular, anticoagulants, diuretics, oxygen therapy and calcium channel blockers.
  - A lung or heart-lung transplant is the treatment of last resort. 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**
  ADEMPAS is one of the specific first-line symptomatic treatments available for class II and III PAH as monotherapy or in combination with endothelin receptor antagonists only.

- **In chronic thromboembolic pulmonary arterial hypertension that is inoperable or persistent/recurrent following surgery (class II or III):**
  The therapeutic management makes use of treatments such as long-term anticoagulation. If the patient is operable, pulmonary thromboendarterectomy is the treatment of choice.
  If this procedure is not possible (distal lesions or comorbidities) or if patients have persistent or recurring symptoms after a thromboendarterectomy, there are currently no alternative treatments. The recommendations to use...
PAH-specific treatments (endothelin receptor antagonists, phosphodiesterase inhibitors and prostacyclin analogues) in these two situations are based on limited data and these proprietary medicinal products do not have Marketing Authorisation in this indication.

**Role of the medicinal product in the therapeutic strategy**

ADEMPAS has a role in the symptomatic treatment of chronic thromboembolic pulmonary hypertension that is inoperable, or persistent or recurrent following surgery.

**Clinical data**

- Two randomised, controlled, double-blind phase III studies have compared the efficacy of riociguat with a titration of up to 2.5 mg 3 times daily with placebo.
- The PATENT-1 study included 443 patients with idiopathic PAH or PAH associated with connective tissue disease, of functional class II or III. The change in 6-minute walk distance at 12 weeks (primary endpoint) was greater in the riociguat 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]).
- The CHEST-1 study included 261 patients with chronic thromboembolic pulmonary hypertension (class II or III), inoperable for 72.4% of them and persistent or recurrent following surgery for 27.6%. The change in 6-minute walk distance at 16 weeks (primary endpoint) 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]).
- The most common adverse events related to riociguat were neurological disorders (vertigo, headaches), gastrointestinal disorders (dyspepsia, nausea, vomiting, diarrhoea), and peripheral oedema and arterial hypotension.

**Special prescribing conditions**

- Orphan medicinal product for hospital prescription, reserved for certain specialists (respiratory medicine, cardiology, internal medicine).

**Benefit of the medicinal product**

In the indication pulmonary arterial hypertension (class II or III):

- The actual benefit* of ADEMPAS is moderate.
- ADEMPAS does not provide a clinical added value** (CAV level V, nonexistent) compared with the other specific therapies for pulmonary arterial hypertension.
- Recommends inclusion on the list of reimbursable products for hospital use.

In the indication chronic thromboembolic pulmonary hypertension that is inoperable or persistent/recurrent after surgery (class II or III):

- The actual benefit* of ADEMPAS is moderate.
- ADEMPAS provides a clinical added value** (CAV level IV, minor) in the absence of an alternative therapy.
- Recommends inclusion on the list of reimbursable products for hospital use.

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* 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”.

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