HAUTE AUTORITÉ DE SANTÉ

RARE DISEASE
New medicinal product
December 2018

TRANSPARENCY COMMITTEE OPINION SUMMARY

ORKAMBI (lumacaftor / ivacaftor), CFTR gene corrector and potentiator

High clinical benefit and minor clinical added value in the management of cystic fibrosis, in patients aged between 6 and 11 years, homozygous for the *F508del* mutation of the CFTR gene.

Main points

- ORKAMBI has now been granted a marketing authorisation for the treatment of cystic fibrosis in patients aged between 6 and 11 years, homozygous for the *F508del* mutation of the CFTR gene.
- The efficacy of ORKAMBI is based exclusively on one intermediate endpoint: improvement in lung clearance index assessed in the short-term (24 weeks) relative to placebo, with no demonstrated impact on quality of life.
- Its safety profile is similar to that observed in adolescents and adults.

Pre-existing indication*

ORKAMBI has already been granted a similar marketing authorisation in patients aged 12 years and above.

Therapeutic strategy

- Respiratory management of cystic fibrosis relies on daily respiratory physiotherapy, along with aerosol therapy using inhaled mannitol (BRONCHITOL) or dornase alfa (PULMOZYME), which provides a modest improvement in respiratory function and in the number of exacerbations requiring antibiotic therapy and whose administration must be followed by a respiratory physiotherapy session.
  Based on the available data, it is not possible to recommend the systematic prescription of inhaled corticosteroids and bronchodilators. A beta-2-mimetic may be proposed in the event of exacerbations, or in the long-term during stable periods, or in nebulised form, with short-acting products, before starting the physiotherapy session, in order to improve bronchial drainage.
  Antibiotic therapy is required in the event of exacerbation or of chronic infection, in successive courses, or as a long-term treatment.
- Nutritional management includes a high-calorie, normal-lipid diet with intake of lipid-soluble vitamins (A, D, E, K) and trace elements (Iron, Zinc, Selenium), sodium chloride supplementation and external compensation for pancreatic insufficiency through the intake of pancreatic extracts.
- Lung, or even liver, transplantation may be proposed in advanced forms of the disease.
- **Role of the medicinal product in the therapeutic strategy**

  ORKAMBI is a basic treatment for cystic fibrosis, used from the outset in patients aged 6 years and over, homozygous for the *F508del* mutation of the CFTR gene. In conjunction with ORKAMBI, symptomatic treatments are maintained or adapted according to the context. Optimum treatment duration is unknown. ORKAMBI tablets must be taken immediately before or after a fat-containing meal or snack.

* This summary does not cover this indication.

Clinical data

- One study versus placebo included 206 patients aged between 6 and 11 years suffering from cystic fibrosis and homozygous for the *F508del* mutation of the CFTR gene. Patients were randomised to receive 100 mg lumacaftor / 125 mg ivacaftor, 2 tablets, administered twice daily (i.e. a total daily dose of 400 mg lumacaftor / 500 mg ivacaftor), or a placebo. During the 24 weeks of treatment and by comparison to the inclusion value, the mean absolute variation in LCI2.5 lung clearance index (primary endpoint) was of -1.01 in the lumacaftor/ivacaftor group, whereas it remained stable in the placebo group (mean absolute intra-group variation of +0.08), i.e. a statistically significant difference of -1.09 (LS mean, CI95% [-1.43; -0.75], p<0.0001).
- At 24 weeks, the adverse events (AEs) considered to be related or potentially related to the treatment, were most frequently of type : cough, abnormal breathing, nausea and increased ALAT and ASAT levels, with no major differences between the 2 groups. A comparable fraction of patients presented with at least one serious AE: 13 patients (12.6%) in the lumacaftor/ivacaftor group and 11 patients (10.9%) in the placebo group. The only serious AE observed in more than 2 patients was an infectious pulmonary exacerbation of cystic fibrosis (lumacaftor/ivacaftor group: 8 patients (7.8%), placebo group: 5 patients (5.0%)); the serious AEs were considered to be related or potentially related to the treatment in 2 and 3 patients respectively (drug interaction and respiratory tract obstructive disorder each in 1 patient from the lumacaftor/ivacaftor group; distal intestinal obstruction, increased ASAT, ALAT and transaminase levels observed in 1 patient from the placebo group).
- The efficacy of ORKAMBI on long-term disease progression is unknown. The impact of this medicinal product on overall disease management and progression cannot be assessed due to the lack of data concerning morbidity and mortality, bacterial colonisation of the lungs or of long-term safety.

Special prescription requirements

- Medicinal product subject to initial half-yearly hospital prescription.
- Unrestricted repeat prescription.

Benefit of the medicinal product

- The actual clinical benefit* of ORKAMBI is high.
- ORKAMBI provides a minor improvement in actual clinical benefit** (IACB IV) in the therapeutic management of cystic fibrosis, including symptomatic treatments.
- Approved for non-hospital pharmacy reimbursement and for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 05 December 2018 (CT-17070) available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a medicinal product consists of its benefit particularly on the basis of its clinical performances and the severity of the disease treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The improvement in actual clinical benefit (IACB) consists of the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the IACB rating from I, major, to IV, minor. An IACB rating of V (equivalent to "no IACB") denotes a "lack of clinical improvement"