BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

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

Minor improvement in the treatment of cystic fibrosis in children aged 12 years and older, homozygous for the F508del mutation of the CFTR gene.

Main points

- ORKAMBI has received a Marketing Authorisation for the treatment of cystic fibrosis in children aged 12 years and older, homozygous for the F508del mutation of the CFTR gene.
- The efficacy of ivacaftor, in combination with lumacaftor, was demonstrated short-term (24 weeks) despite an open-label follow-up until 48 weeks, on an interim endpoint (absolute change in FEV1 value). The improvement observed compared to placebo is modest (3 to 4% depending on the studies).
- The efficacy of this combination on long-term disease progression is unknown. The lack of long-term morbidity, mortality and safety data do not allow the benefit of the medicinal product to be assessed in the overall management and progression of the disease, in particular on the progression of lung bacterial colonization and its resistance to antibiotics.
- The main adverse effects observed were dyspnoea, diarrhoea and nausea.

Therapeutic use

Respiratory treatment of cystic fibrosis is based on:
- daily respiratory physiotherapy,
- aerosol therapy:
  - inhaled dornase alfa (PULMOZYME), which moderately improves respiratory function and the number of exacerbations requiring antibiotic therapy and administration of which must be followed by a session of respiratory physiotherapy.
  - inhaled mannitol (BRONCHITOL) can also be used.
  - the data available do not allow systematic prescription of inhaled corticosteroids and bronchodilators to be recommended. A beta-2-mimetic can be offered in the event of exacerbations, in the long term during a stable period (with regular re-assessment of the clinical benefit), or in nebulisation (with short-acting products) before starting the physiotherapy session, to improve bronchial drainage.
- antibiotic therapy is necessary in the event of an exacerbation or chronic infection, in successive courses or in long-term treatment.

Nutritional treatment consists of a high-calorie, lipid-normal diet, support of lipid-soluble vitamins (A, D, E, K) and trace elements (Iron, Zinc, Selenium), supplementation with sodium chloride and compensation of exocrine pancreatic insufficiency by providing pancreatic extracts.
A lung or even liver transplant is offered in advanced forms.

- Role of the medicinal product in the therapeutic strategy
ORKAMBI is a basic treatment that should be prescribed from the outset in patients with cystic fibrosis aged 12 years and older who are homozygous carriers for the F508del mutation of the CFTR gene. The optimal duration of treatment is unknown.
Clinical data

- In a first study, after 24 weeks of treatment, a significant improvement of the predicted FEV1 value (primary endpoint) was observed with the two dosages of the combination compared with placebo (difference of 4.03 [2.62; 5.44], p<0.0001 and difference of 2.6 [1.18; 4.01], p=0.0003). No statistically significant difference was observed for the secondary endpoints (hierarchical analysis) and in particular on the change in BMI, change in CFQ-R score and number of pulmonary exacerbations.

- In a second study, after 24 weeks of treatment, a significant improvement of the predicted FEV1 value (primary endpoint) was observed with the two dosages of the combination compared with placebo (difference of 2.6 [1.18; 4.06], p<0.0004 and difference of 3.0 [1.56; 4.44], p<0.0001). Regarding the secondary endpoints, there was a statistically significant difference in BMI, with no improvement in CFQ-R score or number of pulmonary exacerbations.

- The grouped analysis of data from these two studies shows statistically significant results, favouring the two groups treated compared to placebo with regard to the primary endpoint (absolute change in FEV1) and the secondary endpoints (relative change in FEV1, BMI, CFQ-R score, response rate ≥ 5% in relative change of FEV1, number of pulmonary exacerbations/year), while the results observed in the secondary endpoints are mostly insignificant in the studies when considered separately. These results must therefore be interpreted with caution.

- In the open-label follow-up study, the results of the second interim analysis on 12 December 2014 include data on all patients who completed 24 weeks of treatment in the phase III and 24-week follow-up in the PROGRESS study, showed continued improvement in the predicted FEV1 value.

Special prescribing conditions

- Medicine for initial six-monthly hospital prescription
- Unrestricted renewal
- Exception drug status

Benefit of the medicinal product

- The actual benefit of ORKAMBI is substantial in the indication of the Marketing Authorisation.

- Given its modest efficacy demonstrated in terms of change in percentage of the predicted FEV1 value compared to placebo, its safety profile and the absence of therapeutic alternative acting directly on the pathophysiopathological mechanism of cystic fibrosis, ORKAMBI provides a minor clinical added value (CAV IV) in the treatment of cystic fibrosis, based on symptomatic treatments, in patients with cystic fibrosis aged 12 years and older and homozygous for the F508del mutation of the CFTR gene.

- Recommends inclusion on the list of reimbursable products for supply by retail pharmacists and for hospital use.

* The actual clinical benefit (ACB) of a 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 ACB, 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".