HAUTE AUTORITÉ DE SANTÉ

RARE DISEASE
New indication
September 2019

TRANSPARENCY COMMITTEE OPINION SUMMARY

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

Substantial clinical benefit and minor clinical added value in the management of cystic fibrosis, in children age 2 years and older who are homozygous for the *F508del* mutation in the CFTR gene.

Key points

- ORKAMBI granules have MA for the treatment of cystic fibrosis in children age 2 years and older who are homozygous for the *F508del* mutation in the CFTR gene
- A phase III, single-arm study essentially assessed the pharmacokinetics (primary endpoint of the 1st part of the study lasting 2 weeks) and safety (primary endpoint for the 2nd part of the study lasting 24 weeks) of ORKAMBI in children age 2 years to 5 years.
- The safety profile of ORKAMBI appears to be acceptable in children in this age group, with hindsight limited to 26 weeks treatment at most in this study.

Pre-existing indication*

- ORKAMBI tablets are indicated for the treatment of cystic fibrosis in children age 6 years and older who are homozygous for the F508del mutation in the CFTR gene

Care pathway

- Cystic fibrosis patient management requires the intervention of a multidisciplinary team (primary care physicians, specialist centres, paramedical team with physiotherapist and nurse). Treatment is symptomatic and life-long. It is based on complementary interventions, especially respiratory and nutritional management and therapeutic education.
- Respiratory management involves:
  - daily respiratory physiotherapy,
  - aerosol therapy, with:
    - inhaled dornase alfa (PULMOZYME), which can be administered in patients over the age of 5, followed by a 30-minute respiratory physiotherapy session.
    - based on the available data, it is not possible to recommend the routine prescription of inhaled corticosteroids and bronchodilators. A beta-2-mimetic may be offered in the event of exacerbations, or in the long-term during stable periods (with regular reassessment of the clinical benefit), or in nebulised form, with short-acting beta-2-mimetics, before starting the physiotherapy session, in order to improve bronchial drainage.
  - antibiotic treatment is required in the event of exacerbation or of chronic infection, in successive courses, or as a long-term treatment.

  The other treatments for cystic fibrosis respiratory disorders are short courses of oral corticosteroids, after a 2-week course of antibiotics prescribed for exacerbation, if there is no clinical and/or functional improvement (expert opinion), or in the case of allergic bronchopulmonary aspergillosis.
  Lung, or even liver transplantation may be offered as a last resort in advanced forms of the disease.

- 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.

* This summary does not cover this indication.

Role of the medicinal product in the care pathway

ORKAMBI granules is first line basic treatment which must be prescribed from the outset in patients age 2 to 5 years with cystic fibrosis and who are homozygous for the *F508del* mutation in the CFTR gene. The optimal treatment course length is not known.

Clinical data

- A single-arm, open-label phase III study assessed pharmacokinetics and safety in 12 children in part A over 15 days and safety in 60 children in part B over 24 weeks. The pharmacokinetic parameters in children were similar to those observed in adults. The efficacy data in children age 2 to 5 years are limited and taken from descriptive analyses of multiple secondary endpoints (mean sweat chloride level, height, weight, BMI, pancreatic and intestinal markers) from which it is difficult to draw conclusions. These data suggest a moderate improvement in the clinical parameters assessed.
- Safety in paediatric patients was similar to that observed in adult patients. During the 24 weeks of treatment, the adverse events observed in at least 10% of patients were cough (63.3%), fever and vomiting (28.3% for each), rhinorrhoea (25.0%), nasal congestion and upper airway infections (16.7%), elevated ALT (13.3%), otitis media and constipation (11.7% for each), diarrhoea and elevated AST (10.0% for each).

Specific prescribing conditions

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

Benefit of the medicinal product

- The clinical benefit* of ORKAMBI is substantial.
- ORKAMBI provides minor clinical added value** (CAV IV) in the treatment of cystic fibrosis in children aged 2 years and older, who are homozygous for the *F508del* mutation in the CFTR gene.
- Positive opinion issued for retail pharmacy reimbursement and for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 18 September 2019 (CT-17846)
available at **www.has-sante.fr**

* The clinical benefit 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 clinical benefit, which may be substantial, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The clinical added value (CAV) corresponds to the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV level from I, major, to IV, minor. A level V CAV (equivalent to "no clinical added value") denotes a "lack of clinical improvement"