HAUTE AUTORITÉ DE SANTÉ

RARE DISEASE
Paediatrics
March 2016

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

KALYDECO (ivacaftor), selective potentiator of the CFTR protein

Substantial therapeutic improvement in the treatment of cystic fibrosis in children aged 2 years and older, weighing less than 25 kg, who have class III mutations of the CFTR gene

Main points

- KALYDECO 50 and 75 mg has Marketing Authorisation in children aged 2 years and older with cystic fibrosis, weighing less than 25 kg, who have one of the following CFTR gene regulation defect mutations (class III): G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R.
- Its efficacy was demonstrated in children aged 6 years and older, who have these mutations, in particular in terms of short- and medium-term improvement of FEV1. The consequences of these results on the evolution of the patients are unknown, but it seems that established pulmonary lesions cannot heal. Based on the lack of data on long-term morbidity and mortality, the benefit of the medicinal product in the overall management of the disease and its evolution remain to be shown.
- The safety profile in children and in adolescents is comparable to that seen in adults.

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

KALYDECO is basic treatment for cystic fibrosis that can be prescribed from the outset in patients aged 2 to 5 years who have one of the following CFTR gene regulation defect mutations: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R. The optimal duration of treatment is unknown.

Clinical data

In an open-label study that studied the safety and kinetics of ivacaftor, the available clinical data (FEV1, height, weight, BMI) come from descriptive analyses. The efficacy of ivacaftor was evaluated as secondary or tertiary endpoints. At 24 weeks, the change from baseline was:

- a reduction in sweat chloride level (n=25/34): -46.86 mmol/l [-57.67; 36.05].
- a weight gain (n=33/34): 1.36 kg [1.16; 1.56].
- an increase in height (n=32/34): 3.3 cm [2.84; 3.68].
- an increase in BMI (n=32/34): 0.32 kg/m^2 [0.13; 0.51].

The mean FEV1 as percentage of the predicted value did not vary compared to the baseline: 87.73% (±16.83%) and after 24 weeks of treatment 87.75% (±22.52%).
In the absence of comparative data versus standard treatments, the benefit of adding ivacaftor compared to standard treatments alone cannot be determined.
In patients aged 2 years to less than 6 years, the most common adverse effects were: nasal congestion (26.5%), upper respiratory tract infections (23.5%), increased transaminases (14.7%), skin rash (11.8%) and bacterial contamination of expectoration (11.8%).
Serious adverse events reported in patients who received ivacaftor were in particular abdominal pain and increased transaminases.

Special prescribing conditions

- Orphan medicinal product
- Medicine for initial six-monthly hospital prescription only
- Prescription reserved for certain specialists (physicians experienced in the treatment of cystic fibrosis).
- Dispensing reserved for certain specialists
- Exception drug status

Benefit of the medicinal product

- The actual benefit* of KALYDECO 25 and 50 mg is substantial in children aged 2 years and older and weighing less than 25 kg.
- As for children aged 6 years and older, KALYDECO provides a substantial clinical added value** (level II) in the treatment of cystic fibrosis in children aged 2 years and older weighing less than 25 kg and who have one of the following CFTR gene regulation defect mutations (class III): G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R.
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

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This document was created on the basis of the Transparency Committee Opinion of 02 March 2016 (CT-14863) and is available at **www.has-sante.fr**

* 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".