HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
27 OCTOBER 2021

The legally binding text is the original French opinion version

ivacaftor / tezacaftor / elexacaftor
KAFTRIO 75 mg/50 mg/100 mg film-coated tablets

ivacaftor
KALYDECO 150 mg film-coated tablets

New indication

Key points

Favourable opinion for reimbursement in the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are heterozygous for the *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene and who have one of the gating mutations or a residual function mutation.

What therapeutic improvement?

Therapeutic improvement in management of cystic fibrosis.

Role in the care pathway?

The management of cystic fibrosis patients requires the intervention of a multidisciplinary team (cystic fibrosis resource and expertise centres, primary care physicians, specialist centres, paramedical team with physiotherapist and nurse). Treatment is symptomatic and life-long. It is based on complementary interventions, in particular respiratory and nutritional management and patient education. Respiratory management involves:

- daily respiratory physiotherapy,

- aerosol therapy, with:

- inhaled dornase alfa (PULMOZYME), for patients aged 5 years and older, which provides a modest improvement in respiratory function and in the number of exacerbations requiring intravenous antibiotic therapy. It must be 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 chronic infection, in successive courses, or as a long-term treatment. The other symptomatic 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 event 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.

There are two medicinal therapies targeting the *F508del* mutation in the CFTR gene and one of the gating mutations or the residual function mutation:

- KALYDECO (ivacaftor) indicated as monotherapy only for the treatment of patients with a gating mutation, i.e. adults, adolescents, and children aged 4 months and older and weighing 5 kg or more with cystic fibrosis who have an *R117H* CFTR mutation or one of the following gating (class III) mutations in the CFTR gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R.*

- KALYDECO (ivacaftor) in combination with SYMKEVI 100 mg/150 mg (tezacaftor/ivacaftor) tablets is the reference treatment for patients aged 6 years and older who are heterozygous for the *F508del* mutation and have one of the following residual function mutations in the CFTR gene: *P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G* et *3849+10kbC→T*.

The optimal treatment duration for these treatments is not known.

Role of the medicinal product in the care pathway

Considering the demonstrated clinical and biological benefit compared to SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor) for patients with a residual function mutation or to KALYDECO (ivacaftor) for patients with a gating mutation, KAFTRIO (ivacaftor/tezacaftor/elexacaftor) in combination with KALYDECO (ivacaftor) is the first-line treatment of cystic fibrosis in patients who are heterozygous for the *F508del* mutation in the CFTR gene and who have one of the gating mutations or a residual function mutation. It is a long-term treatment that should be prescribed from the outset in these patients.

The optimal duration for this treatment is not known.

COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers:

Clinical benefit

◗ Cystic fibrosis is a serious disease that is life-limiting for patients. The impact of this chronic disease on quality of life is particularly high (according to the contribution of the patient association). The *F508del* mutation in the CFTR gene is the most commonly observed mutation and exposes patients to a relatively severe form of cystic fibrosis.

◗ The proprietary medicinal product KAFTRIO (ivacaftor/tezacaftor/elexacaftor) in combination with KALYDECO (ivacaftor) is a curative treatment.

◗ The efficacy/adverse effects ratio of the proprietary medicinal product KAFTRIO (ivacaftor/tezacaftor/elexacaftor) in combination with KALYDECO (ivacaftor) is high.

◗ There are medicinal alternatives with an MA in the indication extension populations, i.e. KALYDECO (ivacaftor) as monotherapy and SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor).

◗ Considering the demonstrated clinical and biological benefit compared to clinically relevant comparators, KAFTRIO (ivacaftor/tezacaftor/elexacaftor) in combination with KALYDECO (ivacaftor) is the first-line treatment of cystic fibrosis in patients who are heterozygous for the *F508del* mutation in the CFTR gene and who have one of the gating mutations or a residual function mutation.

Public health impact

Considering:

- the seriousness of the disease and its low prevalence,
- the partially met medical need,
- the response provided by KAFTRIO (ivacaftor/tezacaftor/elexacaftor) in combination with KALYDECO (ivacaftor) to the identified need in terms of additional impact on morbidity and mortality given the modest clinical benefit of KAFTRIO (ivacaftor/tezacaftor/elexacaftor) in combination with KALYDECO (ivacaftor) demonstrated versus active comparators: ivacaftor or tezacaftor/ivacaftor, with a safety profile that appears to be favourable. Nonetheless, no impact on quality of life has been demonstrated compared to the control group. However, an impact of triple therapy on quality of life is expected given the demonstrated additional clinical benefit.
- the absence of any demonstrated additional impact on the organisation of care of KAFTRIO (ivacaftor/tezacaftor/elexacaftor) in combination with KALYDECO (ivacaftor) with, nonetheless, an expected additional impact given the additional clinical benefit provided by the triple therapy,

KAFTRIO (ivacaftor/tezacaftor/elexacaftor) in combination with KALYDECO (ivacaftor) is likely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of KAFTRIO (ivacaftor/tezacaftor/elexacaftor) in combination with KALYDECO (ivacaftor) is substantial in the MA indication extension.

The Committee issues a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the indication extension and at MA dosages.

- **Recommended reimbursement rate: 65%**

Clinical Added Value

Considering:
- demonstration of a clinically relevant benefit of KAFTRIO (ivacaftor/tezacaftor/elexacaftor) in combination with KALYDECO (ivacaftor) in a randomised, double-blind controlled study versus clinically relevant comparators (ivacaftor or tezacaftor/ivacaftor) in terms of improvement of FEV1 at week 8 (mean within-group difference of +3.7 points, CI95% [2.8; 4.6], p<0.0001 compared to the baseline value),
- demonstration of a biological benefit in terms of sweat chloride (ranked secondary endpoint), with a demonstrated additional effect size versus clinically relevant comparators that had themselves provided significant progress in the management of cystic fibrosis,
- the safety profile of triple therapy, which appears to be favourable,
- the partially met medical need in the indication evaluated,
Despite:
- the absence of a robust demonstration of an impact of triple therapy on quality of life,
the Transparency Committee considers that KAFTRIO (ivacaftor/tezacaftor/ elexacaftor) in combination with KALYDECO (ivacaftor) provides a minor clinical added value (CAV IV) versus active comparators, i.e. ivacaftor for patients with a gating mutation and the tezacaftor/ivacaftor combination for patients with a residual function mutation, in patients 12 years and over who are heterozygous for the *F508del* mutation in the CFTR gene.