



TRANSPARENCY COMMITTEE SUMMARY 30 JUNE 2021

The legally binding text is the original French opinion version

ivacaftor
KALYDECO 150 mg film-coated tablets
tezacaftor/ivacaftor
SYMKEVI 100 mg/150 mg

New indication

ivacaftor
KALYDECO 75 mg film-coated tablets
tezacaftor/ivacaftor
SYMKEVI 50 mg/75 mg

First assessment

► Key points

Favourable opinion for reimbursement in the treatment of patients **aged 6 years and older** who are homozygous for the *F508del* mutation or who are heterozygous for the *F508del* mutation and have one of the mutations in the *CFTR* gene specified in the MA.

► What therapeutic improvement?

Therapeutic improvement in the treatment of cystic fibrosis in patients aged 6 years and older:

- homozygous for the *F508del* mutation,
- or heterozygous for the *F508del* mutation and who have one of the mutations in the *CFTR* gene specified in the MA.

► Role in the care pathway?

The management of cystic fibrosis patients 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, in particular respiratory and nutritional management and patient education.

Role of the medicinal product in the care pathway

As in children aged 12 years and older, SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor) is a long-term treatment that should be prescribed from the outset in patients with cystic fibrosis (CF) aged 6 years and older who are homozygous for the *F508del* mutation or who are heterozygous for the *F508del* mutation and have one of the following mutations in the *CFTR* gene: *P67L*, *R117C*, *L206W*, *R352Q*, *A455E*, *D579G*, *711+3A→G*, *S945L*, *S977F*, *R1070W*, *D1152H*, *2789+5G→A*, *3272 26A→G* and *3849+10kbC→T*.

In patients homozygous for the *F508del* mutation, the SYMKEVI (tezacaftor/ivacaftor) and KALYDECO (ivacaftor) combination is a first-line treatment, like ORKAMBI (lumacaftor/ivacaftor).

In the heterozygous patients concerned by the MA indication, the SYMKEVI (tezacaftor/ivacaftor) and KALYDECO (ivacaftor) combination is the reference treatment.

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

Patients homozygous for the F508del mutation of the CFTR gene aged 6 to 11 years

► Cystic fibrosis is a serious disease that is life-limiting for patients. The *F508del* mutation in the *CFTR* gene is the most commonly observed mutation and exposes patients to a relatively severe form of cystic fibrosis.

► SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor) is a curative treatment.

► The efficacy/adverse effects ratio of SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor) is high.

► There is a therapeutic alternative: ORKAMBI (lumacaftor/ivacaftor).

► SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor) is a long-term treatment that should be prescribed from the outset in patients with cystic fibrosis (CF) aged 6 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene.

Public health impact

Considering:

- the seriousness of the disease,
- its prevalence and incidence,
- the medical need partially met by the proprietary medicinal product ORKAMBI (lumacaftor/ivacaftor),
- the lack of a demonstrated additional impact on morbidity and mortality or quality of life,
- the absence of any demonstrated impact on the organisation of care,
- the partial response to the identified need, in the same way as that observed for children in the higher age group (absence of mortality data but impact on morbidity based on the results of secondary and tertiary endpoints),

as in children aged 12 years and older, SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor) is substantial in the MA indication extension for SYMKEVI (tezacaftor/ivacaftor) 100 mg/150 mg film-coated tablets and KALYDECO (ivacaftor) 150 mg film-coated tablets and in the MA indication for SYMKEVI (tezacaftor/ivacaftor) 50 mg/75 mg film-coated tablets and KALYDECO (ivacaftor) 75 mg film-coated tablets.

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 MA indication extension for SYMKEVI (tezacaftor/ivacaftor) 100 mg/150 mg film-coated tablets and KALYDECO (ivacaftor) 150 mg film-coated tablets and in the MA indication for SYMKEVI (tezacaftor/ivacaftor) 50 mg/75 mg film-coated tablets and KALYDECO (ivacaftor) 75 mg film-coated tablets, and at the MA dosages.

► **Recommended reimbursement rate: 65%**

Patients who are heterozygous for the *F508del* mutation and have one of the following mutations in the *CFTR* (cystic fibrosis transmembrane conductance regulator) gene: *P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G and 3849+10kbC→T* aged 6 to 11 years

► Cystic fibrosis is a serious disease that is life-limiting for patients. The *F508del* mutation in the *CFTR* gene is the most commonly observed mutation and exposes patients to a relatively severe form of cystic fibrosis.

► SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor) is a curative treatment.

► The efficacy/adverse effects ratio of SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor) is high.

► There are no therapeutic alternatives.

► SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor) is a long-term treatment that should be prescribed from the outset in patients with cystic fibrosis (CF) aged 6 years and older who are heterozygous for the *F508del* mutation in the *CFTR* gene and have one of the mutations specified in the MA.

Public health impact

Considering:

- the seriousness of the disease,
- its prevalence and incidence,
- the unmet medical need,
- the lack of a demonstrated additional impact on morbidity and mortality or quality of life,
- the absence of any demonstrated impact on the organisation of care,
- the partial response to the identified need, in the same way as that observed for children in the higher age group (absence of mortality data but impact on morbidity based on the results of secondary and tertiary endpoints),

as in children aged 12 years and older, SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor) is substantial in the MA indication extension for SYMKEVI (tezacaftor/ivacaftor) 100 mg/150 mg film-coated tablets and KALYDECO (ivacaftor) 150 mg film-coated tablets and in the MA indication for SYMKEVI (tezacaftor/ivacaftor) 50 mg/75 mg film-coated tablets and KALYDECO (ivacaftor) 75 mg film-coated tablets.

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► **Recommended reimbursement rate: 65%**

Clinical Added Value

Patients homozygous for the *F508del* mutation of the *CFTR* gene aged 6 to 11 years

Considering:

- the demonstration of a moderate efficacy in terms of absolute change in mean lung clearance index $LCl_{2.5}$ (primary endpoint) at up to 8 weeks of treatment, with a difference of -0.51 points (CI95% [-0.74; -0.29]; $p < 0.0001$) in favour of SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor) compared to placebo in a phase 3 study having included a majority of patients (77.6%) homozygous for the *F508del* mutation in the *CFTR* gene and a minority of patients (22.4%) heterozygous for the *F508del* mutation in the *CFTR* gene,
- the safety profile, which appears to be acceptable in children aged from 6 to 11 years,
- the identified medical need in this rare disease, reported by the patient association,

And despite:

- the exploratory results relative to biological, growth and symptomatic parameters and quality of life for SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor),
- the absence of comparative data versus ORKAMBI (lumacaftor/ivacaftor),

the Committee considers that, as in patients aged 12 years and older, SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor) provides a minor clinical added value (CAV IV) in the therapeutic management of cystic fibrosis in patients aged 6 years and older who are homozygous for the *F508del* mutation.

Patients who are heterozygous for the *F508del* mutation and have one of the following mutations in the *CFTR* (cystic fibrosis transmembrane conductance regulator) gene: *P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G and 3849+10kbC→T* aged 6 to 11 years

Considering:

- the demonstration of a moderate efficacy in terms of absolute change in mean lung clearance index $LCl_{2.5}$ (primary endpoint) at up to 8 weeks of treatment, with a difference of -0.51 points (CI95% [-0.74; -0.29]; $p < 0.0001$) in favour of SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor) compared to placebo in a phase 3 study having included a majority of patients (77.6%) homozygous for the *F508del* mutation in the *CFTR* gene and a minority of patients (22.4%) heterozygous for the *F508del* mutation in the *CFTR* gene,
- the safety profile, which appears to be acceptable in children aged from 6 to 11 years,
- the substantial unmet medical need in the absence of an available alternative for these patients heterozygous for the *F508del* mutation, reported by patient associations,

And despite:

- the exploratory results relative to biological, growth and symptomatic parameters and quality of life for SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor),

the Committee considers that, as in patients aged 12 years and older, SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor) provides a moderate clinical added value (CAV III) in the therapeutic management of cystic fibrosis in patients aged 6 years and older who are heterozygous for the *F508del* mutation and have one of the following mutations in the *CFTR* gene: *P67L*, *R117C*, *L206W*, *R352Q*, *A455E*, *D579G*, *711+3A→G*, *S945L*, *S977F*, *R1070W*, *D1152H*, *2789+5G→A*, *3272 26A→G* and *3849+10kbC→T*.