HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
OPINION
13 MAY 2020

ivacaftor
KALYDECO 150 mg film-coated tablets

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

First assessment

Key points

Favourable opinion for reimbursement in the treatment of patients aged 12 years and older with cystic fibrosis (CF) 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 12 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 combination in the care pathway

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 12 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 et 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 absence of a direct comparison, it is not possible to determine the respective roles of the SYMKEVI (tezacaftor/ivacaftor) and KALYDECO (ivacaftor) combination compared to ORKAMBI (lumacaftor/ivacaftor).
A study conducted over a period of 8 weeks suggests that SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor) may be of benefit for patients having discontinued treatment with ORKAMBI (lumacaftor/ivacaftor) due to respiratory adverse events.
The safety profile of SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor) appears to be favourable based on available data, characterised by adverse events such as headaches, rhinopharyngitis and nausea, more common in the placebo group.
It should be noted that, in view of their respective SPCs, the drug interaction profile of the SYMKEVI (tezacaftor/ivacaftor) and KALYDECO (ivacaftor) combination appears to be different from that of ORKAMBI (lumacaftor/ivacaftor) with, among other differences, the fact that SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor) is not likely to affect the efficacy of hormonal contraceptives.

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

01 COMMITTEE'S CONCLUSIONS

01.1 Clinical benefit

1.1.1 In the treatment of patients with cystic fibrosis aged 12 years and older who are homozygous for the *F508del* mutation

◗ 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 12 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 ORKAMBI (lumacaftor/ivacaftor),
- the lack of elements supporting the absence of a deterioration in the care and/or life pathway in the absence of robust quality of life data,
- the lack of demonstrated impact on the organisation of care (hospitalisation, AEs, etc.),
- the modest response to the identified need in terms of the efficacy of SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor),

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 treatment of patients with cystic fibrosis aged 12 years and older who are homozygous for the *F508del* mutation.

1.1.2 In the treatment of patients with cystic fibrosis aged 12 years and older who are heterozygous for the *F508del* mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (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*

◗ 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 12 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 et 3849+10kbC→T*.

Public health impact

Considering:

- the seriousness of the disease,
- its prevalence and incidence,
- the unmet medical need,
- the lack of elements supporting the absence of a deterioration in the care and/or life pathway and available results in terms of quality of life,
- the lack of demonstrated impact on the organisation of care (hospitalisation, AEs, etc.),
- the substantial response to the identified need in terms of the efficacy of SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor),

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 treatment of patients with cystic fibrosis aged 12 years and older who are heterozygous for the *F508del* mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (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 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 indications and dosages.

01.2 Clinical Added Value

1.2.1 In the treatment of patients with cystic fibrosis aged 12 years and older who are homozygous for the *F508del* mutation

Considering:

- **the demonstration of a moderate efficacy in terms of absolute change in percent predicted FEV_1 up to 24 weeks of treatment (primary endpoint) in favour of SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor) compared to placebo with an intergroup difference of +4.0 points (95% CI [3.1; 4.8], p<0.0001) in a phase III study,**
- **demonstration of a reduction in the rate of pulmonary exacerbations up to 24 weeks of treatment in favour of SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor) compared to placebo, another endpoint of interest in this disease that was a ranked secondary endpoint (0.99/year in the placebo group versus 0.64/year in the tezacaftor/ivacaftor group (i.e., a ratio of 0.65 (95% CI [0.48; 0.88], p=0.0054),**
- **the safety profile of SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor), which appears to be acceptable in this indication,**

but considering,

- **the absence of direct comparison with ORKAMBI (lumacaftor/ivacaftor) due to their concomitant development,**

- **the results of an indirect comparison not enabling unbiased ranking of the 2 treatments in the therapeutic strategy for cystic fibrosis,**
- **the exploratory results in terms of benefit on quality of life of SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor),**

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

1.2.2 In the treatment of patients with cystic fibrosis aged 12 years and older who are heterozygous for the *F508del* mutation and have one of the mutations indicated in the MA

Considering:
- **demonstration of a clinically relevant efficacy in terms of absolute change in FEV_1 (primary endpoint) with an intergroup difference of + 6.8 points (95% CI [5.7; 7.8], p<0.0001) in favour of SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor) compared to placebo in a phase III study,**
- **the result observed for the respiratory domain in the CFQ-R questionnaire (ranked as key secondary endpoint) with an intergroup difference of 11.1, 95% CI [8.7; 13.6], p<0.0001, in favour of SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor) compared to placebo in the same study,**
- **the safety profile of SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor), which appears to be acceptable in this indication,**
- **the unmet medical need in the absence of an available alternative for these patients heterozygous for the *F508del* mutation,**
- **and despite the absence of an interpretable result in terms of efficacy on the rate of pulmonary exacerbations, another endpoint of interest in this disease, assessed in this study as an exploratory endpoint,**

the Committee considers that 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 12 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 et 3849+10kbC→T.*