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Title SYMKEVI / KALYDECO – A Health Technology Assessment

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Reference link to full report in French
https://www.has-sante.fr/jcms/p_3184439/fr/symkevi-/-kalydeco#asmr

Aim

Assessment of SYMKEVI (tezacaftor/ivacaftor) / KALYDECO (ivacaftor) with a view to funding by the French national health insurance system and of its clinical contribution compared to other strategies in the indication treatment of patients with cystic fibrosis, age 12 years and over, homozygous for the F508del mutation or heterozygous for the F508del mutation and carriers of a CFTR gene mutation stated in the MA.

Conclusions of Transparency Committee

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

Clinical Benefit:

- 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.
- The medicinal product 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 aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene.
- SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor) is unlikely to have an additional impact on public health.

Considering all of the above, 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.

Clinical Added Value:

Considering:

- the demonstration of moderate efficacy in terms of absolute change in FEV_1 up to 24 weeks of treatment (primary endpoint) in favour of SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor) compared to the 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 the 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),

SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor) provides, like ORKAMBI (lumacaftor/ivacaftor), low 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.

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

Clinical Benefit:

- 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.
- The medicinal product 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.
- SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor) is unlikely to have an additional impact on public health.

Considering all of the above, 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.

Clinical Added Value:
Considering:
- demonstration of 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 the placebo in a phase III study,
- the result observed for the respiratory domain in the CFQ-R questionnaire (ranked 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 the 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,

SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor) provides 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.

Recommendations

The Transparency Committee issued its approval for the funding of SYMKEVI (tezacaftor/ivacaftor) and KALYDECO (ivacaftor) by the French national health insurance system (private practice and hospital) in the two indications above.

Methods

The assessment of SYMKEVI (tezacaftor/ivacaftor) / KALYDECO (ivacaftor) was founded on evidence-based medicine with a critical analysis of the clinical data.

Written by

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