HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

SUMMARY

18 NOVEMBER 2020

The legally binding text is the original French opinion version

ivacaftor / tezacaftor / elexacaftor

KAFTRIO 75 mg/50 mg/100 mg film-coated tablets

First assessment

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 homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene or heterozygous for F508del in the CFTR gene with a minimal function (MF) mutation.

What therapeutic improvement?

Therapeutic improvement in management.

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.

In patients homozygous for the F508del mutation of the CFTR gene, CFTR protein modulators have been shown to be effective: ORKAMBI (lumacaftor/ivacaftor) and SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor).

In patients heterozygous for the F508del mutation with a minimal function (MF) mutation, before the arrival of KAFTRIO (ivacaftor/tezacaftor/elexacaftor), the care pathway did not include any CFTR modulators.

Role of the combination in the care pathway

KAFTRIO (ivacaftor/ tezacaftor/elexacaftor) 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 or heterozygous for F508del in the CFTR gene with a minimal function (MF) mutation.

In patients heterozygous for the F508del mutation in the CFTR gene with a minimal function (MF) mutation, in the absence of a therapeutic alternative and considering the robust demonstration of its efficacy, KAFTRIO (ivacaftor/tezacaftor/elexacaftor) in combination with KALYDECO (ivacaftor) constitutes the reference treatment.

In the treatment of patients who are homozygous for the F508del mutation in the CFTR gene, given the substantial clinical benefit demonstrated compared to SYMKEVI (tezacaftor/ivacaftor), KAFTRIO (ivacaftor/tezacaftor/elexacaftor) in combination with KALYDECO (ivacaftor) is the first-line treatment.

COMMITTEE'S CONCLUSIONS

Clinical benefit

In the treatment of patients heterozygous for the F508del mutation in the CFTR gene with a minimal function (MF) mutation

◗ 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 KAFTRIO (ivacaftor/ tezacaftor/elexacaftor) in combination with KALYDECO (ivacaftor) is high.

◗ There are no therapeutic alternatives with an MA in this situation.

◗ KAFTRIO (ivacaftor/tezacaftor/elexacaftor) 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 with a minimal function (MF) mutation.

Public health impact

Considering:

- the seriousness of the disease and its low prevalence,
- the unmet medical need in this situation,
- the significant response provided by KAFTRIO (ivacaftor/tezacaftor/elexacaftor) in combination with KALYDECO (ivacaftor) to the unmet medical need, taking into account:
    - the demonstrated additional impact on morbidity and quality of life without any impact demonstrated on mortality to date,
    - the expected significant impact on the care and life pathway of patients (with a reduction in hospitalisations, in particular),

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 treatment of patients with cystic fibrosis aged 12 years and older who are heterozygous for the F508del mutation in the CFTR gene with a minimal function (MF) mutation.
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 treatment of patients with cystic fibrosis aged 12 years and older who are heterozygous for the F508del mutation with a minimal function (MF) mutation and at the MA dosages.

In the treatment of patients who are homozygous for the F508del mutation in the CFTR gene

◗ 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 KAFTRIO (ivacaftor/ tezacaftor/elexacaftor) in combination with KALYDECO (ivacaftor) is high.

◗ There are therapeutic alternatives with an MA: ORKAMBI (lumacaftor/ivacaftor) and SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor).

◗ KAFTRIO (ivacaftor/tezacaftor/elexacaftor) 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 and its low prevalence,
- the medical need partially met by ORKAMBI (lumacaftor/ivacaftor) and SYMKEVI (tezacaftor/ivacaftor) in combination with KALYDECO (ivacaftor) in this situation,
- the significant response provided by KAFTRIO (ivacaftor/tezacaftor/elexacaftor) in combination with KALYDECO (ivacaftor) to the unmet medical need, taking into account:
    - the demonstrated additional impact on morbidity and quality of life without any impact demonstrated on mortality to date,
    - the expected significant impact on the care and life pathway of patients (with a reduction in hospitalisations, in particular),

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

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 treatment of patients with cystic fibrosis aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene and at the MA dosages.

Clinical Added Value

Considering:

- **the robust demonstration of the efficacy of KAFTRIO (ivacaftor/tezacaftor/elexacaftor) in combination with KALYDECO (ivacaftor) on clinically relevant endpoints with a particularly high size effect in terms of absolute change in FEV_1 from the 4th week of treatment and through week 24, especially:**
    - **absolute increase of +14.3 percentage points compared to placebo in patients who are heterozygous for the F508del mutation in the CFTR gene with a minimal function (MF) mutation and,**
    - **absolute increase of +10.2 percentage points compared to tezacaftor/ivacaftor dual therapy, a clinically relevant comparator, in patients homozygous for the F508del mutation;**

- **robust demonstration of a marked improvement in patients' quality of life in terms of absolute change in CFQ-R questionnaire respiratory domain score from the 4th week of treatment and through week 24, assessed as the primary endpoint in one of the three studies (absolute increases of +16 to +20 points depending on the studies) and corroborated by the patient association;**
- **the benefit observed for other clinically relevant secondary endpoints, such as the number of exacerbations and sweat chloride levels;**
- **the safety profile of KAFTRIO (ivacaftor/tezacaftor/elexacaftor) + KALYDECO (ivacaftor) triple therapy, which appears to be acceptable, with only 1% treatment discontinuations due to adverse events, in particular cutaneous and hepatic adverse events, reported in around 10%;**

and despite:

- **the limited period of follow-up in terms of assessment of its efficacy (24 weeks) and safety (36.5 weeks);**

the Committee considers that KAFTRIO (ivacaftor/tezacaftor/elexacaftor) in combination with KALYDECO (ivacaftor) provides a substantial clinical added value (CAV II) in the therapeutic management of cystic fibrosis in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene or heterozygous for F508del in the CFTR gene with a minimal function (MF) mutation.