SUMMARY

ivacaftor/tezacaftor/elexacaftor
ivacaftor

KAFTRIO 60 mg/40 mg/80 mg and 75 mg/50 mg/100 mg, KALYDECO 59.5 mg and 75 mg

granules in sachets

Indication extension

Adopted by the Transparency Committee on 10 April 2024

Summary of opinion

Favourable opinion for reimbursement in "KAFTRIO (ivacaftor/tezacaftor/elexacaftor) granules are indicated in a combination regimen with KALYDECO (ivacaftor) granules for the treatment of cystic fibrosis (CF) in paediatric patients aged 2 to less than 6 years who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. "

Transparency Committee's conclusions

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, as highlighted by 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 a combination regimen with KALYDECO (ivacaftor) is a curative treatment.
- The efficacy/adverse effects ratio is high.
- KAFTRIO (ivacaftor/tezacaftor/elexacaftor) in a combination regimen with KALYDECO (ivacaftor) is the reference treatment that should be prescribed from the outset in paediatric patients with cystic fibrosis (CF) aged 2 to less than 6 years who have at least one *F508del* mutation in the *CFTR* gene.

Public health benefit

Considering:

- the seriousness of the disease and its low prevalence,
- the partially met medical need in the treatment of paediatric patients with cystic fibrosis aged 2 to less than 6 years who are homozygous for the *F508del* mutation, or heterozygous for the *F508del* mutation, and who have a gating mutation in the *CFTR* gene, and the unmet medical need in the treatment of patients heterozygous for the *F508del* mutation and with a minimal function or residual function mutation in the *CFTR* gene,
- the response provided by KAFTRIO (ivacaftor/tezacaftor/elexacaftor) in a combination regimen with KALYDECO (ivacaftor) to the partially met or unmet medical need, depending on the mutation type, taking into account:
- the expected additional impact on morbidity, without any impact demonstrated on mortality to date,
- the expected but not demonstrated additional impact, in the absence of data supplied, on quality of life and patients' care (with a reduction in hospitalisations, in particular) and life pathway,

KAFTRIO (ivacaftor/tezacaftor/elexacaftor) in a combination regimen 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 75 mg/50 mg/100 mg, 60 mg/40 mg/80 mg (ivacaftor/tezacaftor/elexacaftor) granules in sachets in a combination regimen with KALYDECO 59.5 mg, 75 mg (ivacaftor) granules in sachets is substantial in the MA indication.

The Committee issues a favourable opinion for inclusion of KAFTRIO 75 mg/50 mg/100 mg, 60 mg/40 mg/80 mg (ivacaftor/tezacaftor/elexacaftor) granules in sachets and KALYDECO 59.5 mg, 75 mg (ivacaftor) granules in sachets in both the list of covered drugs for outpatients and the list of covered drugs for inpatients approved for use in the indication and at the MA dosages.

Recommended reimbursement rate for inclusion in the list of covered drugs for outpatients: 65%

Clinical Added Value

Considering:

- **the exploratory results of a phase 3 non-comparative trial and its extension, which aimed to assess the safety and pharmacokinetics of KAFTRIO (ivacaftor/tezacaftor/elexacaftor) in a combination regimen with KALYDECO (ivacaftor) in children aged 2 to less than 6 years who are homozygous for the *F508del* mutation, or heterozygous for the *F508del* mutation in the *CFTR* gene and who have a minimal function mutation in the *CFTR* gene, suggesting an efficacy on lung clearance index and sweat chloride level, a biological marker of *CFTR* function, however with limited follow-up,**
- **the acceptable safety profile in children aged 2 years to less than 6 years, which appears to be similar to that observed in older patients,**
- **the need to have access to effective, well-tolerated treatments in this age group,**

and despite:

- **results for episodes of acute respiratory exacerbation assessed following administration of triple therapy only but not prior to its administration,**
- **the heterogeneous and incomplete pancreatic efficacy data suggested by the evolution in faecal elastase,**
- **the heterogeneity of the sweat response observed between homozygous and heterozygous patients,**
- **the absence of results in terms of quality of life,**
- **the absence of comparative data in patients aged 2 to less than 6 years who are homozygous for the *F508del* mutation, or heterozygous for the *F508del* mutation in the *CFTR* gene and who have a gating mutation, indications for which there are clinically relevant comparators,**
- **the need for a safety assessment in this age group with longer follow-up,**

the Committee deems that, as in patients aged 6 years and older, KAFTRIO 75 mg/50 mg/100 mg, 60 mg/40 mg/80 mg (ivacaftor/tezacaftor/elexacaftor) granules in sachets in a combination regimen with KALYDECO 59.5 mg, 75 mg (ivacaftor) granules in sachets provides:

- **a substantial clinical added value (CAV II) in the care pathway for cystic fibrosis in paediatric patients aged 2 to less than 6 years who are homozygous for the *F508del* mutation in the *CFTR* gene, or heterozygous for the *F508del* mutation in the *CFTR* gene and who have a minimal function mutation in the *CFTR* gene.**
- **a minor clinical added value (CAV IV) in the care pathway for cystic fibrosis in paediatric patients aged 2 to less than 6 years who are heterozygous for the F508del mutation in the *CFTR* gene and who have a residual function mutation or a gating mutation.**

The Committee had specified that this study could, in particular, draw on data from the French registry of cystic fibrosis patients.

This study is currently ongoing, supported by the French registry of cystic fibrosis patients, and concerns patients aged 6 years and older (following the Committee's opinion of 11 May 2022 regarding the extension of the indication to patients aged 6 to 11 years); and the pharmaceutical company undertook to submit the results in the 4th quarter of 2024.

The Committee would like the paediatric populations concerned by the present opinion, i.e. patients aged 2 to less than 6 years, to be included in the post-registration study; and that the pharmaceutical company supply the results available in this age group at the same time as the results concerning patients aged 6 years and older.

Following submission of the results scheduled in the 4th quarter of 2024, the Committee will reassess the triple therapy in the indication of its MA, in the light of all the data available.