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2022007497

Our reference
2022007497

Date 22 March 2022
Subject GVS advisory report on elexacaftor/tezacaftor/ivacaftor (Kaftrio®) in combination with ivacaftor (Kalydeco®) – extension of further conditions

Dear Mr Kuipers,

In the letter of 5 January 2022 (reference CIBG-21-03111), the National Health Care Institute was asked to assess whether the further conditions for elexacaftor/tezacaftor/ivacaftor (Kaftrio®) combined with ivacaftor (Kalydeco®) could be extended. The National Health Care Institute has now completed this assessment. The considerations are included in the report attached to this letter.

Background
Patients with cystic fibrosis (CF) can be divided into different subgroups based on their genetic profiles. CFTR modulators are medicinal products that focus specifically on the CFTR gene that plays a crucial role in cystic fibrosis. Kaftrio® and Kalydeco® are CFTR modulators. Kaftrio® is a combination tablet. Each film-coated tablet contains 100 mg elexacaftor, 50 mg tezacaftor and 75 mg ivacaftor. The licensed indication being evaluated is elexacaftor/tezacaftor/ivacaftor (Kaftrio®) in a combined regimen with ivacaftor (Kalydeco®) 150 mg tablets for treating CF in patients aged 12 and older with at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

Kaftrio® combined with Kalydeco® has already been included on List 1B in the Medicine Reimbursement System (GVS) with the following further conditions on List 2. The recommended dose is two tablets of elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg (Kaftrio®) in the morning and one tablet of ivacaftor 150 mg (Kalydeco®) in the evening.

The following further conditions apply for elexacaftor/tezacaftor/ivacaftor (Kaftrio®):
only in combination with ivacaftor for the treatment of cystic fibrosis (CF) patients aged twelve and older who
1. are homozygous for the F508del mutation in the CFTR gene, or
2. are heterozygous for the F508del mutation with a minimal function mutation.

For ivacaftor (Kalydeco®), the following conditions apply:
only for cystic fibrosis (CF) patients

1. with the 'gating mutations' for which ivacaftor is registered,
2. with an R117H mutation for which ivacaftor is registered,
3. six years and older in combination with tezacaftor/ivacaftor who
   a. are homozygous for the F508del mutation in the CFTR gene or
   b. 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, or are
4. aged 12 years and older in combination with elexacaftor/tezacaftor/ivacaftor
   a. homozygous for the F508del mutation in the CFTR gene or
   b. heterozygous for the F508del mutation with a minimal function mutation.

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Assessment of therapeutic value
The National Health Care Institute concludes that the combination therapy for cystic fibrosis in patients aged 12 and older with at least one F508del mutation meets the criterion of established medical science and medical practice. These are patients with a heterozygous F508del mutation plus a gating mutation, a mutation with residual CFTR function or an unknown CFTR mutation. However, there are uncertainties about the long-term effects.

Budget impact analysis
Taking into account the number of patients to be treated with elexacaftor/tezacaftor/ivacaftor combined with ivacaftor, 100% market penetration and 88% patient compliance, extending the further conditions for elexacaftor/tezacaftor/ivacaftor and the ivacaftor monopreparation in the treatment of patients with at least one F508del mutation in the CFTR gene will involve additional costs charged to the pharmacy budget of €24.3 million in the third year. Without substitution, the additional costs charged to the pharmaceutical budget will be €45.0 million in the third year.

Cost-effectiveness
A financial arrangement has already been agreed by the Ministry of Health, Welfare and Sport (VWS) for all current and future indications of elexacaftor/tezacaftor/ivacaftor. In consultation with VWS and the National Health Care Institute's Insured Package Advisory Committee (ACP), it was decided to refrain from a cost-effectiveness analysis for the assessment of the extension of the further conditions of combination therapy for this indication.

Advice
Elexacaftor/tezacaftor/ivacaftor (Kaftrio®) combined with ivacaftor (Kalydeco®) has added therapeutic value compared to standard care. As price agreements have already been made for this indication, inter alia, the National Health Care Institute recommends that you amend the further conditions for elexacaftor/tezacaftor/ivacaftor (Kaftrio®) combined with ivacaftor (Kalydeco®) as stated below, extending them to include the indication evaluated. The National Health Care Institute also recommends that the combination therapy be regularly evaluated based on the start and stop criteria established by the physicians' association. During previous assessments of CFTR modulators, agreements were already reached about this; this assessment will be taken into account.

Expansion of the condition for elexacaftor/tezacaftor/ivacaftor (Kaftrio®)
Only in combination with ivacaftor for the treatment of cystic fibrosis (CF) patients aged twelve and older who have at least one F508del mutation in the CFTR gene.

Expansion of the condition for ivacaftor (Kalydeco®)
Only in combination with elexacaftor/tezacaftor/ivacaftor for cystic fibrosis (CF) patients aged 12 and older who have at least one F508del mutation in the CFTR gene.

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board

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