Zorginstituut Nederland

> Return address PO Box 320, 1110 AH Diemen

Minister of Health, Welfare and Sport
PO Box 20350
2500 EJ THE HAGUE

National Health Care Institute
Care
Medicinal Products

Willem Dudokhof 1
1112 ZA Diemen
PO Box 320
1110 AH Diemen
www.zorginstituutnederland.nl
info@zinl.nl

T +31 (0)20 797 85 55

Contact
Ms N. Stam

2024024787

Date 4 November 2024
Re: GVS advice elexacaftor/tezacaftor/ivacaftor (Kaftrio®) in combination with ivacaftor (Kalydeco®): extension of further conditions

Our reference
2024024787

Dear Ms Agema,

In your letter of 3 September 2024 (CIBG-24-07333), you asked the National Health Care Institute to advise on the extension of the further condition for the reimbursement of elexacaftor/tezacaftor/ivacaftor (Kaftrio®) and ivacaftor (Kalydeco®) for use in patients aged 2 to 5 years with cystic fibrosis (CF) who have at least one F508del mutation in the CFTR gene. This request follows the submission of a complete reimbursement file by the marketing authorisation holder. Elexacaftor/tezacaftor/ivacaftor in combination with ivacaftor is currently reimbursed for patients from the age of 6 and these products are included in different doses on List 1B and List 2 of the
Medicine Reimbursement System (GVS). In addition, the marketing authorisation holder requests that two new pharmaceutical forms for elexacaftor/tezacaftor/ivacaftor, namely 100 mg/50 mg/75 mg granules and 80 mg/40 mg/60 mg granules, and one new strength of an existing pharmaceutical form for ivacaftor, 59.5 mg granules, that were developed for the 2-to-5 year-old patient group, be placed on List 1B.

We will reply to this request in the form of this letter report.

Background
Since 1 January 2022, elexacaftor/tezacaftor/ivacaftor (Kaftrio®) has been included in the Medicine Reimbursement System (GVS) on List 1B, with the following further condition for reimbursement:
Only in combination with ivacaftor for the treatment of cystic fibrosis (CF) patients aged six and older who have at least one F508del mutation in the CFTR gene.

Since 1 June 2015, ivacaftor (Kalydeco®) has been included in the GVS on List 1B, with the following further conditions for reimbursement:
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 six years and older who have at least one F508del mutation in the CFTR gene, in combination with elexacaftor/tezacaftor/ivacaftor.

In November 2023, the *European Medicines Agency* (EMA) approved the extension of the existing indications of elexacaftor/tezacaftor/ivacaftor with ivacaftor for use in CF patients with at least one F508del mutation in the CFTR gene for the age group of 2 to 5 year-olds. This indication is now subject to a request for reimbursement.

The recommended daily dose for patients aged 2 to 5 years depends on the patient's body weight (see Table 1).

Table 1 Dose recommendations for patients aged 2 to 5 years as listed in the SmPC.

Body weight	**Dosage**
10 kg to < 14 kg	Take one sachet elexacaftor 80 mg/tezacaftor 40 mg/ivacaftor 60 mg granules orally in the morning. Take one sachet of ivacaftor 59.5 mg granules orally in the evening. The total daily dose is 80 mg elexacaftor, 40 mg tezacaftor and 119.5 mg ivacaftor.
≥14 kg	Take one sachet elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg granules orally in the morning. Take one sachet of ivacaftor 75 mg granules orally in the evening. The total daily dose is 100 mg elexacaftor, 50 mg tezacaftor and 150 mg ivacaftor.

Conclusion of substantive assessment (see annex)

Assessment of therapeutic value

The assessment of the therapeutic value and the description of the clinical studies are described in the appendix.

Elexacaftor/tezacaftor/ivacaftor (Kaftrio®) in combination with ivacaftor (Kalydeco®) meets the criteria of established medical science and medical practice and has an added therapeutic value compared to lumacaftor/ivacaftor (Orkambi®), ivacaftor (Kalydeco®), and/or standard symptomatic treatment in the treatment of patients aged 2 to 5 with CF with at least one F508del mutation in the CFTR gene. The National Health Care Institute recommends a regular evaluation of the effectiveness of the treatment, to promote the effective use of elexacaftor/tezacaftor/ivacaftor.

Budget impact analysis

A total of 107 children aged between 2 and 5 years old are expected to be treated with elexacaftor/tezacaftor/ivacaftor in combination with ivacaftor per year. A market penetration of 100% is assumed. The costs per patient per year are €178,954. This calculation is based on 100% patient compliance. The total cost of treatment for 107 patients comes to €19,148,095 per year. For some of the patients, other treatment costs will be substituted, which amounts to a total of €9,911,220 based on the list prices. Extension of the further condition elexacaftor/tezacaftor/ivacaftor with ivacaftor in patients with cystic fibrosis aged 2 to 5 with at least one F508del mutation in the CFTR gene is associated with

additional costs of €9.2 million per year charged to the pharmacy budget.

National Health Care Institute
Care
Medicinal Products

Date
4 November 2024

Our reference
2024024787

Cost-effectiveness
The National Health Care Institute has never before ruled on the cost-effectiveness of a medicinal product in an indication extension based on age. The marketing authorisation holder did provide a cost-effectiveness analysis demonstrating that elexacaftor/tezacaftor/ivacaftor in combination with ivacaftor is not cost-effective in patients aged 2 to 5 years. The National Health Care Institute notes that the comparative treatment in the cost-effectiveness analysis provided does not adequately reflect the current Dutch practice and that no effects on pulmonary function in children aged 2 to 5 years have been applied in the analysis. This results in an incorrect estimate of the cost-effectiveness. During previous indication extensions of elexacaftor/tezacaftor/ivacaftor (Kaftrio®) in combination with ivacaftor, no cost-effectiveness analysis was performed because your predecessor had concluded a single price arrangement for several indications, including indication extensions to other genotypes and age categories. The National Health Care Institute has, for the reasons mentioned above, not assessed the cost-effectiveness analysis for the current indication extension. Instead, it bases its advice on the cost-effectiveness of elexacaftor/tezacaftor/ivacaftor (Kaftrio®) in combination with ivacaftor for patients aged 2 to 5 on the advice previously given in 2021 regarding this treatment for patients aged 12 and older. At the time, the National Health Care Institute recommended a price reduction of at least 75%. For the current indication extension, the National Health Care Institute also recommends a price reduction of at least 75% for elexacaftor/tezacaftor/ivacaftor (Kaftrio®) in combination with ivacaftor.

A more extensive explanation is described in the annex.

Advice
Elexacaftor/tezacaftor/ivacaftor (Kaftrio®) in combination with ivacaftor (Kalydeco®) meets the criteria of established medical science and medical practice and has an added therapeutic value compared to the standard treatment for patients aged 2 to 5 with cystic fibrosis who have at least one F508del mutation in the CFTR gene.

The National Health Care Institute therefore recommends that the List 2 conditions of elexacaftor/tezacaftor/ivacaftor (Kaftrio®) in combination with ivacaftor are to be extended, provided that the following conditions are met:

- A price reduction of at least 75 percent for elexacaftor/tezacaftor/ivacaftor in combination with ivacaftor; the National Health Care Institute advises you to renegotiate with the manufacturer for a price agreement for all future CFTR modulators. The National Health Care Institute also advises the Minister to negotiate about future indication expansions. This should take into account the fact that the cost of lifetime treatment with ELX/TEZ/IVA in combination with IVA will increase if patients can start treatment earlier due to an indication expansion.
- Reaching agreement with the physicians' association on the appropriateness for the effective use of the treatment.
- Long-term data is collected by the physicians' association to evaluate the effectiveness and safety of elexacaftor/tezacaftor/ivacaftor in combination with ivacaftor for patients aged 2 to 5.

National Health Care Institute
Care
Medicinal Products

Date
4 November 2024

Our reference
2024024787

Adjustment of the further condition for elexacaftor/tezacaftor/ivacaftor
Only in combination with ivacaftor for the treatment of cystic fibrosis (CF) patients aged **two** years and older who have at least one F508del mutation in the CFTR gene.

Adjustment of the further condition for ivacaftor
For patients **two** years and older who have at least one F508del mutation in the CFTR gene, in combination with elexacaftor/tezacaftor/ivacaftor.

Yours sincerely,

Mark Janssen
Chairperson of the Executive Board