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Our reference
2023035652

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Date 11 December 2023
Re: GVS advice lumacaftor/ivacaftor extension further condition for use in CF patients aged 1 to 2 years

Dear Mr Kuipers,

In your letter of 23 October 2023 (CIBG-23-06208), you asked the National Health Care Institute to advise on the extension of the further condition for the reimbursement of lumacaftor/ivacaftor (Orkambi®) for application in patients aged 1 to 2 years with cystic fibrosis having a homozygous F508del mutation in the CFTR gene. In addition, the marketing authorisation holder also requests that a new dose of an existing pharmaceutical form, developed for the patient population aged 1 to 2 years, be included in List 1B.

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

Background
Since November 2017, lumacaftor/ivacaftor (Orkambi®) has been included in the Medicine Reimbursement System (GVS) on List 1B, subject to further reimbursement conditions:
Only for the treatment of cystic fibrosis (CF) patients aged two years and older who are homozygous for the F508del mutation in the CFTR gene.

In April 2023, the European Medicines Agency (EMA) approved the extension of the existing indication of lumacaftor/ivacaftor to include the use for CF patients aged 1 to 2 years who are homozygous for the F508del mutation in the CFTR gene. This indication is now subject to a request for reimbursement.

Conclusion of substantive assessment (See appendix)
Assessment of therapeutic value
The assessment of the therapeutic value and the description of the clinical studies are described in the annex.

Lumacaftor/ivacaftor meets the criteria of established medical science and medical practice, and has an added value compared to standard symptomatic treatment for patients aged 1 to 2 years with cystic fibrosis who are homozygous for the F508del mutation in the CFTR gene.

Budget impact analysis
A total of 17 children aged between 1 and 2 years old are expected to be treated

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with lumacaftor/ivacaftor per year. The budget impact analysis assumes that this number will remain stable over the next 3 years. This means that there are as many patients added annually as patients ageing out of the age group after a year. A market penetration and patient compliance of 100% has been assumed. Lumacaftor/ivacaftor costs €128,326 per patient per year. The total treatment costs for 17 patients come to € 2,181,538 per year. As treatment with lumacaftor/ivacaftor is applied in addition to standard symptomatic therapy, no substitution of current treatments will occur. Extension of lumacaftor/ivacaftor for CF patients aged 1 to 2 years who are homozygous for the F508del mutation (F/F) in the CFTR gene will be accompanied by additional costs to the pharmaceutical budget of €2.2 million.

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 lumacaftor/ivacaftor. In consultation with the Ministry of Health, Welfare and Sport, 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
Lumacaftor/ivacaftor meets the criteria of established medical science and medical practice, and has an added value over standard symptomatic treatment for patients 1 to 2 years old with cystic fibrosis who are homozygous for the F508del mutation in the CFTR gene. Since price agreements have already been made for this indication, among others, the National Health Care Institute recommends that you amend the further condition for lumacaftor/ivacaftor as below and extend it with the assessed indication. The National Health Care Institute also recommends regularly evaluating the combination therapy 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.

Extension of further condition for lumacaftor/ivacaftor
Only for the treatment of cystic fibrosis (CF) patients aged *one year or older* who are homozygous for the F508del mutation in the CFTR gene.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board

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Appendix

Assessment of the extension of the further conditions

Lumacaftor/ivacaftor (Orkambi®) (from now on LUM/IVA) for the treatment of children aged 1 to 2 years with cystic fibrosis with a homozygous F508del mutation (F/F) has not been previously evaluated by the National Health Care Institute[1-3].

Cystic fibrosis in children aged 1 to 2 years

Cystic fibrosis (CF) is a rare, incurable autosomal recessive hereditary disorder caused by a mutation in the CFTR gene. The CFTR gene codes for the production of the protein "cystic fibrosis transmembrane conductance regulator", a protein that ensures the transport of chloride over the epithelial cells' membrane. This transport is important for the balance of salt and water on surfaces in the body such as the surface of the lung and the pancreas. The salt and water that are excreted by the epithelial cells form mucus, which has an important function: flushing out dust, bacteria and viruses in the lungs. Mutations in the CFTR gene can lead to poorly functioning chloride channels and problems with chloride and water transport across membranes in many organs. As a result, some glands will produce a thick, sticky mucus.[1-5]

In young children, recurrent respiratory tract infections, reduced pancreatic function, gastrointestinal symptoms such as gallstones and delayed growth are most dominant. Young children often still have good pulmonary function, but as they get older, their lungs become increasingly damaged, and their pulmonary function continues to decrease.[5, 6]

The severity of the disease depends on the type of mutation. CF patients who are homozygous for the F508del mutation in the CFTR gene have little to no functioning CF protein and therefore have a severe form of the disease. The main cause of death is irreversible damage to the lungs. The life expectancy of CF patients is around 40 to 50 years.[1-3]

Treatment

The treatment of CF is described in the 2020 national quality standard for cystic fibrosis. This was prepared by the Dutch Association of Physicians for Pulmonary Diseases and Tuberculosis (NVALT), the Dutch Paediatric Association (NVK) and the Dutch Cystic Fibrosis Foundation (NCFS). The standard treatment for CF patients consists of a combination of medicinal products aimed at combating pulmonary infections and inflammations (antibiotics), clearing of mucus (mucolytics) and improvement of the nutritional status (pancreatic enzyme supplementation therapy). Vaccination is recommended to reduce the risk of infection. Depending on the genotype of the CFTR gene, patients use a CFTR modulator in addition to this standard treatment.[4, 5]

For CF patients aged 1 to 2 years with an F/F mutation, the use of a CFTR modulator is currently not reimbursed, so these patients are only treated with the standard symptomatic treatment.

Study data

Study 122 (VX16-809-122) is a multicentre, single-arm, open-label phase III study in CF patients aged 1 to 2 years with an F/F mutation in the CFTR gene.

Inclusion criteria were proven CF (sinopulmonary disease, gastrointestinal symptoms or worsening nutritional status and/or sweat chloride concentration ≥ 60 mmol/l) and a stable disease. Patients with liver cirrhosis, organ or stem cell transplantation were excluded. Patients were also excluded if they had a pulmonary exacerbation or respiratory infection in the 28 days prior to the study. The study consisted of two parts: Part A was designed to determine the pharmacokinetics of LUM/IVA in children aged 1 to 2 years and was used to determine the dose. Part B of the study was aimed at assessing the safety and effectiveness of LUM/IVA in children aged 1 to 2 years. All patients in the study were treated with LUM/IVA. Patients weighing 7 to 9 kg received lumacaftor 75 mg twice daily and ivacaftor 94 mg twice daily, patients with a body weight of 9 to 14 kg received lumacaftor 100 mg twice daily and ivacaftor 125 mg twice daily, and patients with a body weight of 14 kg and over received lumacaftor 150 mg twice daily and ivacaftor 188 mg twice daily. The treatment duration of Part B was 24 weeks. The primary outcome measure of Part B was safety and tolerability; secondary outcome measures were the sweat chloride concentration and pharmacokinetic parameters of lumacaftor and ivacaftor. Additional outcome measures from this study included body mass index (BMI), body height, body weight, pulmonary exacerbation rate, CF-related hospitalisations, pancreatic function determined by faecal elastase-1 (FE-1) and serum immunoreactive trypsin and trypsinogen (IRT) and chronic intestinal inflammation determined by faecal calprotectin. Patients who completed the study were asked to participate in the long-term extension study of 96 weeks (study 124 (VX19-809-124)).[7]

Desirable effects
In study 122, treatment with LUM/IVA in children aged 1 to 2 years with CF and an F/F mutation resulted in a clinically relevant reduction in sweat chloride concentration (-29.1 mmol/L [95% CI: 34.8;-23.4]). In addition, LUM/IVA caused a statistically significant increase in FE-1 concentration (73.1 µg/g [95% CI: 29.4;116.8]) and a statistically significant reduction in serum IRT (-295.5 µg/l [95% CI: -416.6;-174.5]). There was also a statistically significant reduction in faecal calprotectin concentration (-106.63 mg/kg [95% CI: -180.60;-32.66]). The study found an estimated annual event rate of 0.60 (SD:1.5) for pulmonary exacerbations and 0.20 (SD:0.7) for CF-related hospitalisations. No differences were found in growth parameters compared to the normal growth of children aged 1 to 2 years. After 2 weeks washout, the sweat chloride concentration, FE-1 concentration, serum IRT value and faecal calprotectin concentration returned to the baseline value.[7, 6]

Since there was no control group in study 122, it is not possible to make a statement about the effectiveness of LUM/IVA compared to placebo. Also, it is not possible to comment on the effect of LUM/IVA on pulmonary exacerbation rates, as the event rate for pulmonary exacerbations in children aged 1 to 2 years with CF and an F/F mutation not taking LUM/IVA is not known.[7, 6]

The reduction in sweat chloride concentration observed in children aged 1 to 2 years with an F/F mutation was similar to the reduction in sweat chloride concentration observed in children aged 2 to 5 years with an F/ F mutation (-31.7 mmol/ l) and at least equivalent to the reduction in sweat chloride observed in children aged 6 to 11 years with an F/F mutation and in children aged 12 years and over and adults with an F/F mutation (-24.8 mmol/ l and -21.7 mmol/ l, respectively).[7, 6]

Adverse effects
The use of LUM/ IVA is generally safe and it was well tolerated by patients. The most common adverse effects were coughing, CF-related pulmonary exacerbations, pyrexia, vomiting, upper respiratory tract infection, constipation, ear infection, a runny nose and a positive pseudonomas test. The majority of reported adverse effects were mild or moderate in severity and were most often symptoms that can be expected in patients with cystic fibrosis. One patient (2.2%) in Part B of Study 122 had a potential intervention-related severe adverse effect (distal intestinal obstruction). In Part A of study 122, none of the patients experienced a severe adverse effect. One patient (7.1%) in Part A and one patient (2.2%) in Part B discontinued treatment due to an adverse effect (skin rash and ASAT/ALAT increase). No adverse effects were found that were not already observed in the age group of 2 years and older.[7, 6]

Discussion
Treatment with LUM/IVA resulted in a clinically relevant reduction in sweat chloride concentration in children aged 1 to 2 years with an F/F mutation[7]. In addition, treatment with LUM/IVA may have improved pancreatic function, and children treated with LUM/IVA showed a normal growth[7]. Since there was no control group, it is not possible to make a statement about the effectiveness of LUM/IVA compared to placebo. It is also not possible to make a statement about the effect of LUM/IVA on the number of pulmonary exacerbations.

In study 122, pulmonary function and lung clearance were not measured, whereas in studies in adults and older children, these are the primary outcome measures[6]. Due to the lack of these data, the extent to which LUM/IVA prevents lung damage at this age is somewhat unclear. In previous assessments for indication extensions of CFTR modulators in children, the physicians association indicated that measuring pulmonary function in young children is difficult[8, 9]. Young children still have good pulmonary function, and so their pulmonary function is not expected to improve significantly but to remain at most the same. According to the physicians association, a reduction in sweat chloride concentration in young children could potentially predict the extent to which the disease progression of CF is improved by CFTR modulators. At present, it is not yet clear what the precise effect of the reduction in sweat chloride concentration is on the morbidity and mortality of CF. The physicians association has indicated that CF patients who reach a 'normal' sweat chloride concentration (< 30 mmol/l) may no longer have further progression of CF. Especially in children, this reduction in the sweat chloride concentration could mean that their lungs are not further affected and that they also no longer have a reduced pancreatic function.

The reduction in sweat chloride concentration in children aged 1 to 2 years with an F/F mutation found in study 122 was similar to that observed in patients aged 2 years and older[6]. Since the reduction in sweat chloride concentration levels is similar between patients aged 2 years and older and patients aged 1 to 2 years, it can be concluded with sufficient confidence that the effectiveness of LUM/IVA in children aged 1 to 2 years with CF and an F/F mutation is similar to that of LUM/IVA in adults and children aged 2 years and older with the same mutation.

In young children with CF, reduced pancreatic function reduces growth and as a result children with CF have a stunted growth, compared to their peers. In study 122, LUM/IVA improved pancreatic function and appeared to normalise exocrine

pancreatic function in four children after treatment with LUM/IVA[7]. In the absence of a control group and a clinical relevance limit, it is not possible to make a firm statement about the precise effect of LUM/IVA on pancreatic function in young children. This was also concluded during the previous assessment of LUM/IVA in children aged 2 to 5 years with the same mutation[3].

LUM/IVA is well tolerated by children aged 1 to 2 years and the side effects are generally mild to moderate in severity. The adverse effects of LUM/IVA in children aged 1 to 2 years with an F/F mutation are similar to those in adults.[6]

Conclusion
Lumacaftor/ivacaftor (Orkambi®) meets the criteria of established medical science and medical practice, and has an added therapeutic value over standard symptomatic treatment for patients aged 1 to 2 years with cystic fibrosis who are homozygous for the F508del mutation in the CFTR gene.

The National Health Care Institute also recommends a regular evaluation of the effectiveness of the treatment, to promote the appropriate use of lumacaftor/ivacaftor.

References

1. ZIN. GVS-advies lumacaftor/ivacaftor (Orkambi®) bij cystic fibrose (CF) bij patiënten van 12 jaar en ouder die homozygoot zijn voor de F508del mutatie in het CFTR-gen. 2016.
2. ZIN. GVS-advies lumacaftor/ivacaftor (Orkambi®) voor cystische fibrose van 6 tot en met 11 jaar. 2018.
3. ZIN. GVS-advies lumacaftor/ivacaftor (Orkambi®) uitbreiding bijlage 2 voorwaarde voor toepassing bij kinderen van 2 t/m 5 jaar. 2019.
4. NVALT and CBO. Richtlijn diagnostiek en Behandeling Cystic fibrosis. 2008.
5. NVALT, NVK AND NCFS. Kwaliteitsstandaard Cystic Fibrosis. 2020. Assessed on 04-09-2023 at https://richtlijnendatabase.nl/richtlijn/kwaliteitsstandaard_cystic_fibrosis_cf/startpagina_-_cf.html.
6. EMA. Orkambi-H-C-3954-X-0078-G: EPAR - Assessment Report - Extension. 2023. Assessed on 04-09-2023 via https://www.ema.europa.eu/en/documents/variation-report/orkambi-h-c-3954-x-0078-g-epar-assessment-report-extension_en.pdf.
7. Rayment JH, Asfour F, Rosenfeld M, et al. A Phase 3, Open-Label Study of Lumacaftor/Ivacaftor in Children 1 to Less Than 2 Years of Age with Cystic Fibrosis Homozygous for F508del-CFTR. Am J Respir Crit Care Med 2022; 206: 1239-47.
8. ZIN. GVS-advies uitbreiding bijlage 2 voorwaarden tezacaftor/ivacaftor (Symkevi®) in combinatie met ivacaftor (Kalydeco®). 2021.
9. ZIN. GVS-advies elexacaftor/tezacaftor/ivacaftor (Kaftrio®) met ivacaftor (Kalydeco®) monopreparaat:uitbreiding nadere voorwaarden. 2022.