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Our reference
2021008420

Date 25 May 2021
Subject Ivacaftor (Kalydeco®) extension of further conditions applicable to cystic fibrosis (CF) patients aged 6 months and older with one R117H mutation

Dear Ms van Ark,

In your letter of 16 March 2021 (CIBG-21-01601), you asked the National Health Care Institute to carry out a review to extend the further conditions for reimbursement of ivacaftor (Kalydeco®). The application for the extension of the further conditions is related to patients 6 months and older with cystic fibrosis and an R117H mutation in the CFTR gene.

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

Current situation
Since 1 June 2015, ivacaftor (Kalydeco®) has been included in the medicine reimbursement system (GVS) on List 1B, subject to further reimbursement conditions.

The current further conditions for ivacaftor are:
1 Only for cystic fibrosis (CF) patients with 'gating mutations' for which ivacaftor is registered, or
2 Only in combination with tezacaftor/ivacaftor for the treatment of cystic fibrosis (CF) patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene.

Extension of the indication of ivacaftor for CF patients with an R117H mutation
In September 2015, the European Medicines Agency (EMA) approved the extension of the existing ivacaftor indication for adult CF patients with an R117H mutation. In June 2020, EMA extended this indication for CF patients aged between 4 months and 18 years who have an R117H mutation. To date, the marketing authorisation holder has not applied to extend the further conditions of ivacaftor (Kalydeco®) for adult CF patients with an R117H mutation.

Conclusion of substantive assessment (See appendix)
Ivacaftor has a therapeutic added value compared to placebo for the treatment of adult patients with cystic fibrosis and an R117H mutation in the CFTR gene. Evidence of activity for ivacaftor in CF patients aged 6 months to 17 years with an

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R117H mutation is very limited. However, the National Health Care Institute recommends, on the basis of indirect evidence (sweat chloride concentration) and evidence found in adults, to extend the List 2 conditions for this group as well. Since the effect of ivacaftor for individual CF patients with an R117H mutation varies widely, the National Health Care Institute recommends that the treatment with ivacaftor should be regularly evaluated on the basis of the start and stop criteria established by the NVALT and NCFS.

It is assumed that 5 patients with the above indication will be treated with ivacaftor. Based on 100% market penetration and 88% patient compliance, treatment costs will be €162,803 per patient per year. Increasing the further condition of ivacaftor for patients with cystic fibrosis aged 6 months and older with an R117H mutation in the CFTR gene is accompanied by additional costs of €0.8 million charged to the pharmaceutical budget.

National Health Care Institute advice
Ivacaftor (Kalydeco®) is already included on list 1B with further conditions. Based on the new research results, we advise you to extend the List 2 conditions for Kalydeco® with the application for CF patients aged 6 months and older with an R117H mutation in the CFTR gene. This extension to the further condition involves additional costs of €0.8 million.

Extension further condition for ivacaftor
"Only for cystic fibrosis (CF) patients with the R117H mutation for which ivacaftor is registered"

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board

Appendix: Assessment of the extension of the further condition and the budget impact analysis

Appendix

Assessment of the extension of the further conditions
Ivacaftor for patients aged 6 months and older with cystic fibrosis and an R117H mutation in the CFTR gene has not been previously assessed by the National Health Care Institute.[1]

Cystic fibrosis in patients with an R117H mutation in the CFTR gene
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 saline and water balance on surfaces such as in the lungs and the pancreas. The saline 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 poor chloride channels and problems with chloride and water transport across membranes in many organs. As a result, some glands will produce a thick, tough mucus.[2-4]

The R117H mutation is a mutation in the CFTR gene; it is classified as a Class IV mutation. These are mutations that cause a disturbed conductivity of the chloride channel, resulting in reduced chloride transport. The R117H mutation also has the properties of a "gating" mutation and therefore also causes a defect in the opening of the channel. Unlike other mutations in the CFTR gene, it is not obvious for the R117H mutation that the mutation will actually cause CF. For example, the R117H-7T and R117H-9T variants are milder than the R117H-5T variant. Patients with these variants have an almost normal sweat-chloride concentration and no symptoms or only mild symptoms of CF.[5, 6]

In young CF patients with an R117H mutation, the disease focuses on the reduced pancreas function and gastrointestinal symptoms such as gall stones and delayed growth in young children. In addition, CF patients often get recurrent pulmonary infections from early childhood. At a later age (from 17 years), CF patients with an R117H mutation will start to have a progressive decline in pulmonary function. This differs from the progression of CF in patients with other mutations such as the "gating" mutation in which the decline of pulmonary function is already occurring in childhood. Patients with an R117H mutation experience a gradual decline in pulmonary function in adulthood, which means that the life expectancy of this group is equal to the life expectancy of patients with other mutations. Because the deterioration of the pulmonary function takes place at a later age, young children generally have mild symptoms and still show good pulmonary function. As a result, patients with an R117H mutation are often diagnosed with CF at a later age.[5, 6]

Currently, there are 47 CF patients with an R117H mutation in the Netherlands. According to the physicians association and the patients' association, 5 patients are currently eligible for ivacaftor treatment. The physicians association has indicated that mainly adults with this mutation will be treated with ivacaftor and that for the time being it will be unlikely for children and adolescents with this mutation to be treated with ivacaftor.[4]

Treatment
The treatment of CF is described in the 2020 national quality standard for cystic fibrosis. This was written 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 also use a CFTR modulator in addition to this standard treatment.[2, 3]

For CF patients with an R117H 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 110 (KONDUCT) is a double-blind, multicentre, randomized, placebo-controlled phase III study in CF patients aged 6 years and older with an R117H mutation in the CFTR gene. Inclusion criteria were a ppFEV1 between 40-90% (patients ≥ 12 years) or between 40-105% (patients 6-11 years) and a body weight of at least 25 kg. Patients were treated with 150mg ivacaftor twice daily for a period of 24 weeks. At the end of the study, there was a wash-out period of 3 to 4 weeks. Patients who completed the study were asked to participate in the open-label extension study (study 112), in which all patients were treated with ivacaftor for 104 weeks. The primary outcome measure of the study was the pulmonary function measured as the percentage predicted forced expiratory volume in 1 second (ppFEV1). Secondary outcome measures of this study were the sweat-chloride concentration, the Cystic Fibrosis Questionnaire-revised (CFQ-R) symptom score, the time to first pulmonary exacerbations and the safety and tolerability of the treatment.[7]

Study 112 (KONTINUE) is a multicentre, open-label phase III extension study open to CF patients with a non-G551D gating mutation, an R117H mutation or a residual function mutation who had previously participated in an RCT with ivacaftor (for CF patients with an R117H mutation, this was study 110). All participants were given ivacaftor in the recommended daily dose. The follow-up of this study was 104 weeks. The primary outcome measure of this study was the long-term safety and tolerability of ivacaftor. The secondary outcome measure of this study was the long-term effectiveness of ivacaftor. For long-term effectiveness, the pulmonary function (ppFEV1), the number of pulmonary exacerbations, the sweat-chloride concentration, Body Mass Index (BMI) and the CFQ-R symptom score were measured.[8]

For children aged under 6, only single-arm phase III studies have been conducted for CF patients with a 'gating' mutation, and no studies have included CF patients with an R117H mutation. These studies are study 108 (KIWI) (children aged 2 to 6 with a 'gating' mutation)[9, 10] and study 124 (ARRIVAL) (children aged 4 to 24 months with a 'gating' mutation)[11].

Favourable effects
In the scientific studies, there were differences between the effectiveness of ivacaftor in adults and children with cystic fibrosis and an R117H mutation in the CFTR gene, therefore the results for adults and children will be discussed separately.

<u>Adults</u>
The treatment with ivacaftor in adults resulted in the 110 study in a clinically relevant improvement of pulmonary function (ppFEV1) compared to placebo (+

5.0% [95% BI: 1.15 to 8.78]).[7, 6] In addition, treatment with ivacaftor resulted in a clinically relevant improvement of the CFQ-R symptom score (12.6 [95% BI: 5.82 to 20.25]) and there was a statistically significant decrease in the sweat-chloride concentration compared to placebo (-21.9 [95% BI: -26.46 to -17.28]).[7, 6] In the open-label extension study (study 112), the effects on these outcome measures remained similar during the entire study of 104 weeks.[8, 5]

The number of pulmonary exacerbations was determined only for the entire patient population. No significant difference was found in the number of pulmonary exacerbations compared to placebo for the CF patients aged 6 years and older with an R117H mutation. The number of patients to be admitted due to a pulmonary exacerbation decreased, as well as the number of patients who used an intravenous antibiotic due to a pulmonary exacerbation.[7]

Children aged 6 to 18 years
The treatment with ivacaftor in patients aged between 6 and 11 years in the 110 study resulted in a clinically relevant decline in pulmonary function (-6.3% [95% BI: -11.96 to -0.71]). There was also a deterioration in the CFQ-R symptom score (12.6 [95% BI: 5.82 to 20.25]). There was a significant decrease in the sweat-chloride concentration compared to placebo (-27.6 [95% BI: -37.16 to -18.10]) and it was approximately equal to the decrease in the sweat chloride concentration found in adults with the same mutation. Due to insufficient evidence, it was not possible to determine the effectiveness of ivacaftor in CF patients aged between 12 and 18 years with an R117H mutation.[7, 5]

In the open-label extension study (study 112), after 48 weeks of treatment, ivacaftor caused a clinically relevant improvement of the pulmonary function (+4.0% (SD 2.5)). However, due to the lack of a control group, the placebo-controlled effect on the pulmonary function for patients aged between 6 and 11 years is still uncertain. The decrease in the sweat chloride concentration remained approximately equal throughout the entire study period to the value found in study 110.[5, 8]

Children aged 6 months to 6 years
Currently, no studies have been performed for the treatment of CF patients aged between 6 months and 6 years with an R117H mutation. The EMA has made its assessment for this indication with the use of studies conducted in children with a "gating" mutation (study 108 and study 124). These single arm studies did not measure the pulmonary function, but they did show a decrease in the sweat chloride concentration that was similar to the value found in CF patients aged 6 years and older with the same mutation. These studies also found that there was a positive effect of ivacaftor on the BMI and the faecal elastane-1, which is a marker for improved pancreatic function.[5, 9-11]

Undesirable effects
The use of ivacaftor was generally safe and well tolerated by patients. The most common undesirable effects were pulmonary exacerbations, coughing, headache, nasal congestion, sinusitis, nasopharyngitis, oropharyngeal pain, abdominal pain and wheezing breathing. The majority of reported undesirable effects were mild to moderate in nature and were generally symptoms that can be expected in patients with cystic fibrosis. Four patients (12%) in study 110experienced a serious undesirable effect and two patients in study 112 experienced a serious

medication-related undesirable effect. There were no significant differences in side effects between adults and children. In addition, the undesirable effects that were encountered correspond to the undesirable effects that were previously found in studies with CF patients with a G551D mutation or a non-G551D "gating" mutation.[5, 6]

Discussion
Ivacaftor in adult CF patients with an R117H mutation caused a clinically relevant improvement in pulmonary function. There was also a clinically relevant improvement in the CFQ-R symptom score in adult patients, and a significant reduction in the sweat chloride concentration.[6, 7]

In children aged between 6 and 18 with CF and an R117H mutation, there is uncertainty about the placebo-controlled effect of ivacaftor on the pulmonary function. A statistically significant reduction in the sweat chloride concentration was found, which was approximately equal to the reduction found in adult patients. In addition, no improvement in the CFQ-R symptom score was observed.[7, 8, 5]

In both adults and children, no significant difference was found in the occurrence of pulmonary exacerbations, compared to placebo. Fewer patients were hospitalised because of a pulmonary exacerbation and an intravenous antibiotic was used less frequently for a pulmonary exacerbation.[7]

CF patients with an R117H mutation experience less effectiveness from ivacaftor than CF patients with a 'gating' mutation. Both the effect on pulmonary function and on the sweat chloride concentration is substantially lower than in patients with a 'gating' mutation.[5, 6] This can be explained by the difference in the course of this disease. CF patients with an R117H mutation often have a lower sweat chloride concentration and a better pulmonary function than CF patients with a 'gating' mutation.[5, 6] This is especially visible in children and adolescents aged between 6 and 18 years who have a very good pulmonary function compared to their peers with a 'gating' mutation. In children and adolescents, therefore, it is not expected that there will be a significant improvement in pulmonary function when using ivacaftor.[5, 6]

In children aged between 6 and 11 years with cystic fibrosis and an R117H mutation, a decline in pulmonary function compared to placebo was even observed.[5] In the study, there was only one single patient who actually experienced a decline in pulmonary function due to a pulmonary exacerbation. Because there were very few young patients in this study, the result can be significantly affected by a single patient. [5] In addition, no deterioration in pulmonary function was observed in the extension study and even this single patient experienced an improvement in pulmonary function after prolonged use of ivacaftor.[5] However, due to the lack of the control group in the extension study, it is not possible to determine the actual placebo-controlled effect on pulmonary function.

Currently, there are no results for CF patients aged under 6 years with an R117H mutation.[5] Based on the results found in CF patients aged 4 months and older with a 'gating' mutation, the EMA has concluded that the effectiveness of ivacaftor in adults can be extrapolated to the effectiveness of ivacaftor in children.[5] They

determined this through the sweat chloride concentration.[5] Also in CF patients with an R117H mutation, the effects on the sweat chloride concentration are almost similar for adult and paediatric patients aged 6 to 11 years. And so it could be concluded that the effectiveness of ivacaftor in children with an R117H mutation is equal to the effectiveness of ivacaftor in adults.

At this moment, it is not yet known what the exact clinical relevance is of the reduction of the sweat chloride concentration due to ivacaftor.[5] In the future, it may become more clear what the effect of the sweat chloride concentration is on the disease progression of CF.[5] The physicians association has indicated that CF patients who reach a 'normal' sweat chloride concentration (< 30 mmol/l) may no longer have further CF progression. Especially in children, this reduction in the sweat chloride concentration could mean that their lungs are not further affected by the disease and that they no longer have a reduced pancreatic function. In addition, the physicians association states that treatment with ivacaftor will mainly be intended for adults with this specific mutation.

There is a large individual variation in the effectiveness of ivacaftor in adults with an R117H mutation. In the studies, for example, patients with an F508del mutation plus an R117H mutation seemed to have less benefit from treatment with ivacaftor monotherapy.[6] That is why the National Health Care Institute recommends that the treatment with ivacaftor should be regularly evaluated on the basis of the start and stop criteria established by the NVALT and NCFS, to promote the effective use of ivacaftor.

Conclusion
Ivacaftor has a therapeutic added value compared to placebo for the treatment of adult patients with cystic fibrosis and an R117H mutation in the CFTR gene. There is uncertainty about the placebo-controlled effect of ivacaftor on the pulmonary function in children and adolescents aged from 6 months with cystic fibrosis and an R117H mutation in the CFTR gene. Nevertheless, the National Health Care Institute recommends, on the basis of indirect evidence (sweat chloride concentration) and evidence found in adults, to extend the List 2 conditions for this group as well. Since the effectiveness of ivacaftor for individual patients varies widely, the National Health Care Institute recommends that the treatment with ivacaftor should be regularly evaluated on the basis of the start and stop criteria established by the NVALT and NCFS.

Budget impact analysis
This report estimates the (additional) costs, resulting from the extension of the additional List 2 conditions of ivacaftor (Kalydeco®) to be borne by the pharmaceutical budget, thus allowing the treatment of CF in patients with an R117H mutation from the age of 6 months. Currently, ivacaftor is reimbursed for patients with 'gating mutations' for which ivacaftor is registered, and in combination with tezacaftor/ivacaftor for patients aged 12 years and older who are homozygous for the F508del mutation. Guiding principles for the BIA are: the registered indication, the potential number of patients eligible for treatment with the medicinal product, the pharmacy purchase price (AIP), the dosage of the medicinal product, the duration of the treatment, and the possible substitution of the current treatment.

Currently, patients under 18 years old with this mutation are not treated with

CFTR modulating therapy; the entire therapy is documented in the pharmacotherapeutic report.

Number of patients, substitution and cost per patient.
In the Netherlands, 5 CF patients under the age of 18 are known to have the R117H-5T variant, and are eligible for ivacaftor treatment. The 2019 NCFS register shows that there are 47 patients in the Netherlands with the R117H mutation.[12] The National Health Care Institute assumes that this will remain the same and, on average, no patients will be added in the coming years.

There is no substitution for these patients.

Ivacaftor (Kalydeco®) is available as film-coated tablets with a strength of 150 mg per tablet and as a granulate of 25 mg, 50 mg and 75 mg. The AIP of a tablet or a bag of granulate (regardless of the dosage) of ivacaftor is €273.43.

Infants of at least 6 months old, toddlers and children, adolescents and adults should be dosed in accordance with Table 1.[13]

The recommended dose for adults, adolescents and children aged 6 years and older with a body weight of 25 kg or more is one ivacaftor 150 mg tablet, to be taken orally every 12 hours (300 mg total daily dose) with fat-containing food.

Table 1: Dose schedule for ivacaftor

Gewicht	Dosis	Totale dagelijkse dosis
≥ 5 kg tot < 7 kg	25 mg granulaat, om de 12 uur oraal ingenomen met vetbevattend voedsel	50 mg
≥ 7 kg tot < 14 kg	50 mg granulaat, om de 12 uur oraal ingenomen met vetbevattend voedsel	100 mg
≥ 14 kg tot < 25 kg	75 mg granulaat, om de 12 uur oraal ingenomen met vetbevattend voedsel	150 mg
≥ 25 kg	Zie de SPC voor Kalydeco tabletten voor meer informatie	

Weight	Dose	Total daily dose
≥ 5 kg to < 7 kg	25 mg of granulate, taken orally every 12 hours with fat-containing food	50 mg
≥ 7 kg to < 14 kg	50 mg of granulate, taken orally every 12 hours with fat-containing food	100 mg
≥ 14 kg to < 25 kg	75 mg of granulate, taken orally every 12 hours with fat-containing food	150 mg
≥25 kg	See the SPC for Kalydeco tablets for more information	

An 88% patient compliance is assumed, in line with the National Health Care Institute's past assessment of CFTR modulators. [1]

Based on a daily treatment schedule of two tablets or sachets of granulate ivacaftor (365 days a year), the medical costs for an adult or child are: (€253.43*365 *88% =) €162,803 per patient per year.

Assumptions

- -There 5 CF patients known to have the R117H-5T variant; they are eligible for ivacaftor treatment.
- -It is assumed that these 5 Dutch patients will be treated with ivacaftor.
- -Patients compliance is 88%.
- -The prevalence of patients with an R117H-5T mutation remains the same and no new patients are added.

Budget impact analysis and conclusion

Based on 5 patients, the total budget impact is 5*€162,803 = €814,015 per year; there is no distinction between years 1, 2 and 3 because the National Health Care Institute bases its analysis on equal prevalence and no incidence of patients.

In conclusion, an adjustment of the List 2 conditions for ivacaftor is expected to lead to 5 new patients that are eligible for ivacaftor. The corresponding budget impact is estimated at €0.8 million.

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