Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Resolutions on the Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Lumacaftor/Ivacaftor (new therapeutic indication: cystic fibrosis, patients aged 2–5 years)

of 15 August 2019

Contents

1. Legal basis

According to Section 35a, paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. Approved therapeutic indications,
2. Medical benefit,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Treatment costs for statutory health insurance funds,
6. Requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA shall pass a resolution on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient combination lumacaftor/ivacaftor was listed for the first time on 15 December 2015 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

On 15 January 2019, Orkambi® received marketing authorisation for a new therapeutic indication classified as a major variation of type 2 according to Annex 2 No. 2a to Regulation (EC) number 1234/2008 of the Commission from 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

On 8 February 2019, the pharmaceutical company submitted in due time (i.e. at the latest within four weeks after the pharmaceutical company has been informed of the approval for a new therapeutic indication) a dossier in accordance with Section 4, paragraph 3, number 2 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the Federal Joint Committee (G-BA) on the active ingredient combination lumacaftor/ivacaftor (LUM/IVA) with the new therapeutic indication “Orkambi® granules are indicated for the treatment of cystic fibrosis (CF) in children aged 2 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene.

In the present procedure only the patient group between 2 and 5 years of age is considered. The treatment of cystic fibrosis in children from 6 years of age who are homozygous for the *F508del* mutation in the CFTR gene was the subject of the benefit assessment of LUM/IVA in a resolution dated 2 August 2018. The treatment of cystic fibrosis in patients from 12 years of age who are homozygous for the *F508del* mutation in the CFTR gene was the subject of the benefit assessment of LUM/IVA in a resolution dated 2 June 2016.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 15 May 2019, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of lumacaftor/ivacaftor compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods[1] was not used in the benefit assessment of lumacaftor/ivacaftor.

In light of the above and taking into account the comments received and the oral hearing, the G-BA has arrived at the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of lumacaftor/ivacaftor (Orkambi®) in accordance with the product information

Orkambi® granules are indicated for the treatment of cystic fibrosis (CF) in children aged 2 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene.

The present resolution relates exclusively to the newly approved therapeutic indication of 15 January 2019 (i.e. children from 2 to 5 years of age with cystic fibrosis who are homozygous for the F508del mutation in the CFTR gene).

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Patients aged 2 to 5 years with cystic fibrosis who are homozygous for the *F508del* mutation.

- Best supportive care.

  Best supportive care (BSC) is defined as the therapy that ensures the best possible, patient-individual optimised, supportive treatment to alleviate symptoms and improve the quality of life (especially antibiotics for pulmonary infections, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy (in the sense of the HeilmittelRichtlinie (Remedies Directive)), making full use of all possible dietary measures).

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication according to the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

zu 1. The following medicinal products are approved for symptomatic therapy of CF: Aztreonam (Cayston®)[2], ceftazidim, colistimethate, dornase alfa (Pulmozyme®)[2], mannitol (Bronchitol®)[2], pancreatin, tobramycin[2].

zu 2. In the treatment of CF, nutritional measures and the support of respiratory function are generally considered as non-medicinal treatments.

zu 3. The G-BA has not passed any resolutions for the patient group “children aged between 2 and 5 years” to be considered in this therapeutic indication.
For patients who are homozygous for the *F508del* mutation in the CFTR gene, the following resolutions of the G-BA on a change of the AM-RL: Annex XII – Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V are available:
for the active ingredient combination tezacaftor/ivacaftor, there is considerable additional benefit for the patient group “patients aged 12 and over” (resolution of 16 May 2019).
For LUM/IVA there is a hint of an non-quantifiable additional benefit for the patient group “children from 6 to 11 years of age” (resolution of 2 August 2018). For the patient group “patients 12 years and older” with cystic fibrosis, an indication of considerable additional benefit was found for LUM/IVA (resolution of 2 June 2016).

zu 4. The generally accepted state of medical knowledge for the indication was established by means of a search for guidelines and systematic reviews of clinical studies. According to the current state of medical knowledge, there is no specific standard therapy for patients with CF aged 2 years and older. For patients with CF aged 2 years and older, the aforementioned medicinal and non-medicinal therapy options are available for symptomatic therapy. In the evidence provided, these are recommended for symptomatic therapy of CF, in particular, antibiotic therapy of pulmonary infections (ceftazidine, colistimethate, tobramycin), inhalation of medicinal products (mannitol, thornase alfa), enzyme substitution for pancreatic insufficiency (pancreatin), and

[2] Not approved for children aged 2 years and older with CF

nutritional therapy and support of respiratory function (e.g. through physiotherapy). CF is thus treated individually for each patient to alleviate symptoms and improve the quality of life in the sense of best supportive care (BSC). The designation of best supportive care as appropriate comparative therapy in the present procedure for patients aged 2 years and older with CF who are homozygous for the *F508del* mutation in the CFTR gene is an editorial adjustment compared with the appropriate comparator therapy "best possible symptomatic therapy (BST)" determined for treatment with LUM/IVA in 6- to 11-year-old children with CF who are homozygous for the *F508del* mutation in the CFTR gene. Treatment with BST is equivalent to best supportive care in clinical implementation. In the following, the term best supportive care is chosen.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of lumacaftor/ivacaftor (LUM/IVA) is assessed as follows:

For LUM/IVA for the treatment of cystic fibrosis in children aged 2 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene, the transfer of evidence to the paediatric population at the age of 2 to 5 years provides a hint of an additional benefit compared with the appropriate comparative therapy. However, this is non-quantifiable because the scientific data basis currently does not permit this.

Justification:

For the benefit assessment of LUM/IVA in children aged 2 years and older with cystic fibrosis who are homozygous for the *F508del* mutation in the *CFTR* gene, the pharmaceutical company extrapolates the results of LUM/IVA treatment in children 6 to 11 years of age (study VX14-809-109, hereinafter 109) and in patients ≥ 12 years of age (studies VX12-809-103 and VX12-809-104, hereinafter 103 and 104) to the target population of 2- to 5-year-old children. Furthermore, the pharmaceutical company uses the results of the paediatric study VX15-809-115 (hereinafter referred to as 115) for the extrapolation.

Based on the direct comparison study 109, the benefit assessment for LUM/IVA in children with cystic fibrosis from 6 years of age who are homozygous for the *F508del* mutation in the *CFTR* gene has already been performed. In a resolution dated 2 August 2018, a hint for a non-quantifiable additional benefit was established for LUM/IVA versus best supportive care (BSC) for the patient group aged 6 years and older.

Based on direct comparison studies 103 and 104, the benefit assessment for LUM/IVA in patients with cystic fibrosis from 12 years of age who are homozygous for the *F508del* mutation in the *CFTR* gene has already been performed. In a resolution dated 2 June 2016, a indication of a considerable additional benefit was established for LUM/IVA versus BSC for the patient group aged 12 years and older.

Study 115 of 2- to 5-year-old children with cystic fibrosis is a single-arm, open-label Phase III study. All patients in study 115 received LUM/IVA. Study 115 is divided into two phases. In Part A (N = 12) of study 115, patients received LUM/IVA over a period of 15 days. In Part B (N=60) of study 115, the duration of treatment with LUM/IVA was 24 weeks. Only Part B of Study 115 is considered for the present benefit assessment. The dosage of LUM/IVA followed the specifications in the product information.

Study 115 included patients 2 to 5 years of age with confirmed CF diagnosis and a homozygous *F508del* mutation in the CFTR gene. The patients included had to have a body weight of ≥ 8 kg and a sweat chloride value of ≥ 60 mmol/L at the time of the screening. Patients with severely limited liver function were excluded from the study population.

The data presented in the dossier shows that the patients enrolled in the study received comprehensive symptomatic medical treatment during the course of the study containing among others: dornase alfa, sodium chloride, pancreatin and salbutamol as well as antibiotics, food supplements and corticosteroids. Overall, it is to be assumed that at least one appropriate (stable) basic therapy with mucolytics and pancreas enzymes took place.

The primary endpoint of study 115 was adverse events. In addition, endpoints of the category mortality and morbidity were collected. Data on health-related quality of life were not collected in Study 115.

The evaluation report of the European Medicines Agency (EMA)[3] states that Study 115, which comprised 2- to 5-year-old children, is subject to a number of restrictions, including the lack of a comparator arm and the short duration of the study because of the slow disease progression. At the same time, it is recognised that cystic fibrosis with homozygous *F508del* mutation in the CFTR gene is a severe chronic disease with a progressive course and that only supportive therapy alternatives exist for 2- to 5-year-old children. Patients aged between 2 and 5 years usually have only mild symptoms. Thus, no significant changes in patient-relevant endpoints (e.g. pulmonary exacerbations) between baseline and week 24 can be expected for this patient population. As described in the EMA assessment report, the results of the studies of 6- to 11-year-old children and patients 12 years and older support those of the paediatric study for 2- to 5-year-old children.

In the studies of children aged 2 years and older and 6 years and older, LUM/IVA showed comparable efficacy based on the results for the endpoint Lung Clearance Index ($LCI_{2.5}$). For the population of 6- to 11-year-old children, study 109 at week 24 showed a statistically significant advantage of LUM/IVA for the endpoint $LCI_{2.5}$ compared with the appropriate comparator therapy (best supportive care). For the population of 2- to -5-year-old children, the same effect trend could be shown for $LCI_{2.5}$ from baseline to week 24; however, this did not reach statistical significance. For the sub-population of 2- to 5-year-old children with a body weight of ≥ 14 kg, there was a statistically significant advantage over baseline at week 24 for the endpoint $LCI_{2.5}$ (MD [95% CI]): −0.76 [−1.45; −0.08]; p = 0.032). Furthermore, it can be inferred from the comments of the EMA that LUM/IVA in 2- to 5-year-old children has an acceptable side-effect profile comparable to the populations of 6- to 11-year-old children and patients ≥ 12 years.

In summary, the EMA concludes that there is an identical underlying genetic cause of the disease and a comparable pathophysiology, and, based on the study data for patients aged 6 years and older and 12 years and older and the study for patients aged 2 years and older, the pharmacokinetic parameters and efficacy and safety of LUM/IVA are comparable.

For the G-BA, these findings form the minimum prerequisite for a transfer of evidence. The appropriate comparator therapy for children aged 2 years and older as well as for children from 6 years of age and for patients from 12 years of age defined by the G-BA is identical (best supportive care), thereby providing a decisive criterion for transfer of evidence in the benefit assessment. The standards to be applied for the recognition of evidence based on a low degree of evidence also take into account the particularities and limitations associated with the conduct of paediatric clinical trials.

The results on the efficacy and safety of LUM/IVA in children aged 2 years and older show largely the same effect trend compared to the results of the studies for the population of 6- to 11-year-old children and patients ≥ 12 years of age.

In study 115 (2- to 5-year-old children), no deaths occurred under treatment with LUM/IVA.

in Study 115, no statistically significant difference between LUM/IVA and baseline was found for the endpoint forced expiratory volume in one second (FEV_1%). For the endpoint Lung

[3] Assessment Report; EMA/843650/2018

Clearance Index ($LCI_{2.5}$; absolute change), there was no statistically significant difference between LUM/IVA and baseline (MD [95% CI]) based on the mean difference: −0.58 [−1.17; 0.02]; p = 0.056). In a sub-population of 2- to 5-year-old children with a body weight of ≥ 14 kg, LUM/IVA showed a statistically significant advantage over baseline at week 24 for the endpoint $LCI_{2.5}$ (MD [95% CI]): −0.76 [−1.45; −0.08]; p = 0.032). In Study 115, both the BMI and the BMI z-score were used as endpoints. BMI is a measure of weight adjusted for height. BMI z-scores are standardised BMI values adjusted for child age and sex, which, in contrast to BMI, are considered an important parameter for assessing developmental disorders in paediatric patients with cystic fibrosis. Study 115 showed a statistically significant difference between LUM/IVA and baseline (MD [95% CI]): 0.29 [0.14; 0.45]; p < 0.001); however, it cannot be conclusively assessed to what extent the improvement in BMI z-score shown can be attributed to the increasing age and development of the patients.

Pulmonary exacerbations, above all those that lead to admission to hospital, present a clinically relevant endpoint and are to be viewed as patient-relevant. In study 115, 25 pulmonary exacerbations occurred per 29 patient years under treatment with LUM/IVA. The study shows that pulmonary exacerbations in children aged 2 to 5 years are not very common events.

In study 115, four hospitalisations because of CF occurred per 29 patient years.

Endpoints of the endpoint category health-related quality of life were not investigated in Study 115.
In Study 115, adverse events occurred in 59 patients (98.3%), serious adverse events occurred in 4 patients (6.7%), and severe adverse events (≥ grade 3) occurred in 5 patients (8.3%). A total of three patients (5.0%) discontinued treatment with LUM/IVA because of adverse events.

Based on the data provided by the pharmaceutical company for the benefit assessment, no statement can be made regarding the course of the disease in 2- to 5-year-old children receiving the appropriate comparator therapy of best supportive care.

The resolution of 2 August 2018 determined that the additional benefit of LUM/IVA over best supportive care in patients 6 years of age and older with cystic fibrosis who are homozygous for the *F508del* mutation in the *CFTR* gene was largely due to the advantages of LUM/IVA compared to the appropriate comparative therapy in the morbidity surrogate endpoint Lung Clearance Index ($LCI_{2.5}$). The same effect trend from baseline to week 24 was also shown for study 115 (children aged 2 to 5 years) for the endpoint $LCI_{2.5}$. $LCI_{2,5}$ is considered a surrogate endpoint. Based on the study submitted by the pharmaceutical company, it cannot be concluded that $LCI_{2.5}$ is a valid surrogate parameter for patient-relevant endpoints. However, in the patient population under consideration, composed of young children with, as yet, relatively few symptoms, it is only possible to measure an influence on the course of the disease to a very limited extent. In the written statement procedure, it became clear that it is established practice in this therapeutic area to use the endpoint $LCI_{2.5}$ to record early changes in cystic fibrosis. $LCI_{2.5}$ is therefore included as a relevant endpoint for the benefit assessment of patients with cystic fibrosis in the age group under consideration here. There is a lack of long-term data for $LCI_{2.5}$, and the validity of the results with regard to longer-term effects (e.g. as pulmonary exacerbations and symptomatic improvement) is limited.

The resolution of 2 June 2016 determined that the additional benefit of LUM/IVA over best supportive care in patients 12 years of age and older with cystic fibrosis who are homozygous for the *F508del* mutation in the *CFTR* gene was largely due to the advantages of LUM/IVA compared to the appropriate comparative therapy (best supportive care) in the pulmonary exacerbations endpoint. Both study 115 of 2- to 5-year-old children and study 109 of 6- to 11-year-old children found that pulmonary exacerbations were not frequent events in the very young patient population (2–5 years and 6–11 years) still largely free of symptoms.

In view of the fact that the underlying genetic cause of the disease is identical and therefore pathophysiologically comparable, and on the basis of the study data for 2- to 5-year-old children, which reveals largely similar effects to the results from studies involving 6 to 11-year-old children and patients ≥ 12 years, and in view of the fact that the appropriate comparator therapies are identical for the three populations, the G-BA considers that the observed additional benefit in the "$LCI_{2.5}$" endpoint can be transferred from the 6- to 11-year old to the 2- to 5-year old population, even though the extent of this benefit cannot be quantified because of the uncertainties described.

With regard to the reliability of this finding, the G-BA rules that there is a hint for a non-quantifiable additional benefit.

Overall assessment/conclusion

Based on the transfer of evidence from the studies for children 6–11 years of age and patients 12 years of age and older to the population of 2- to 5-year-old children, the G-BA establishes an additional benefit of LUM/IVA for children aged 2 years and older with cystic fibrosis who are homozygous for the *F508del* mutation in the *CFTR* gene. Based on the criteria in Section 5, paragraph 7 of the AM-NutzenV, the G-BA classifies the extent of the additional benefit as non-quantifiable.

Taking into account the non-availability of treatment alternatives for 2- to 5-year-old children, the severity of the disease, the progressive course of the disease, and the therapeutic objective of the treatment, the G-BA rules that there is a hint for a non-quantifiable additional benefit for the endpoint "$LCI_{2.5}$" compared with the appropriate comparator therapy best supportive care despite the available clear limitations of the evidence provided. However, this is not quantifiable because the scientific data basis does not permit this.

2.1.4 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of LUM/IVA has its legal basis in Section 35a, paragraph 3, sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In this case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment pursuant to Section 35a, paragraph 1 SGB V.

In the written statement procedure, the pharmaceutical company indicated that recruitment is ongoing for the randomised controlled trial VX15-809-121 (LUM/IVA vs placebo) for 2- to 5-year-old children with cystic fibrosis who are homozygous for the *F508del* mutation in the *CFTR* gene. The final results of the study are expected in May 2021.

These final results of the VX15-809-121 study are also relevant for the benefit assessment according to Section 35a SGB V. In order to evaluate these relevant data on LUM/IVA treatment for patient-relevant endpoints, the G-BA considers it sufficient to limit the validity of this resolution to 1 October 2021.

In accordance with Section 3, number 5 AM-NutzenV in conjunction with Chapter 5, Section 1, paragraph 2, number 7 VerfO, the procedure for the benefit assessment of LUM/IVA shall recommence when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the day of expiry of the deadline to prove the extent of the additional benefit of LUM/IVA (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, number 5 VerfO). The possibility that a benefit assessment for LUM/IVA can be carried out at an earlier point in time for other reasons (*cf.* Chapter 5, Section 1 paragraph 2 VerfO) remains unaffected by this. In principle, an extension may be granted if it is justified and clearly demonstrated that the period of the limitation is not sufficient.

2.1.5 Summary of the assessment

The present assessment concerns the benefit assessment of of lumacaftor/ivacaftor (LUM/IVA) in the new therapeutic indication. LUM/IVA is indicated for the treatment of cystic fibrosis (CF) in children aged 2 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene.

Based on the data provided by the pharmaceutical company for the benefit assessment, no statement can be made regarding the course of the disease in 2- to 5-year-old children receiving the appropriate comparator therapy of best supportive care.

The resolution of 2 August 2018 determined that the additional benefit of LUM/IVA over best supportive care in patients 6 years of age and older with cystic fibrosis who are homozygous for the *F508del* mutation in the *CFTR* gene was largely due to the advantages of LUM/IVA compared to the appropriate comparative therapy in the morbidity surrogate endpoint Lung Clearance Index ($LCI_{2.5}$). The same effect trend from baseline to week 24 was also shown for study 115 (children aged 2 to 5 years) for the endpoint $LCI_{2.5}$. The $LCI_{2,5}$ is considered a surrogate endpoint. Based on the study submitted by the pharmaceutical company, it cannot be concluded that $LCI_{2.5}$ is a valid surrogate parameter for patient-relevant endpoints. However, in the patient population under consideration, composed of young children with, as yet, relatively few symptoms, it is only possible to measure an influence on the course of the disease to a very limited extent. In the written statement procedure, it became clear that it is established practice in this therapeutic area to use the endpoint $LCI_{2.5}$ to record early changes in cystic fibrosis. $LCI_{2.5}$ is therefore included as a relevant endpoint for the benefit assessment of patients with cystic fibrosis in the age group under consideration here. There is a lack of long-term data for $LCI_{2.5}$, and the validity of the results with regard to longer-term effects (e.g. as pulmonary exacerbations and symptomatic improvement) is limited.

The resolution of 2 June 2016 determined that the additional benefit of LUM/IVA over best supportive care in patients 12 years of age and older with cystic fibrosis who are homozygous for the *F508del* mutation in the *CFTR* gene was largely due to the advantages of LUM/IVA compared to the appropriate comparative therapy (best supportive care) in the pulmonary exacerbations endpoint. Both study 115 (2- to 5-year-old children) and study 109 (6- to 11-year-old children) found that pulmonary exacerbations were not frequent events in the very young patient population (2–5 years and 6–11 years) still largely free of symptoms.

In view of the fact that the underlying genetic cause of the disease is identical and therefore pathophysiologically comparable, and on the basis of the study data for 2- to 5-year-old children, which reveals largely similar effects to the results from studies involving 6 to 11-year-old children and patients ≥ 12 years, and in view of the fact that the appropriate comparator therapies are identical for the three populations, the G-BA considers that the observed additional benefit in the "$LCI_{2.5}$" endpoint can be transferred from the 6- to 11-year old to the 2- to 5-year old population, even though the extent of this benefit cannot be quantified because of the uncertainties described.

With regard to the reliability of this finding, the G-BA rules that there is a hint for a non-quantifiable additional benefit.

Based on the transfer of evidence from the studies for children 6–11 years of age and patients 12 years of age and older to the population of 2- to 5-year-old children, the G-BA establishes an additional benefit of LUM/IVA for children aged 2 years and older with cystic fibrosis who are homozygous for the *F508del* mutation in the *CFTR* gene. Based on the criteria in Section 5, paragraph 7 of the AM-NutzenV, the G-BA classifies the extent of the additional benefit as non-quantifiable.

Taking into account the non-availability of treatment alternatives for 2- to 5-year-old children, the severity of the disease, the progressive course of the disease, and the therapeutic objective of the treatment, the G-BA rules that there is a hint for a non-quantifiable additional benefit for the endpoint "$LCI_{2.5}$" compared with the appropriate comparator therapy best

supportive care despite the available clear limitations of the evidence provided. However, this is not quantifiable because the scientific data basis does not permit this.

2.2 Number of patients or demarcation of patient groups eligible for treatment

To ensure consistency in analysing patient numbers whilst taking into account the most recent resolution (16 May 2019) on the benefit assessment of drugs with new active ingredients as per Article 35a SGB V in the indication "cystic fibrosis (CF) in patients aged12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene", the G-BA calculates patient numbers as follows:

The information on the number of patients is based on the target population in statutory health insurance (SHI).

A total patient group of currently approx. 8000 patients with cystic fibrosis in Germany is assumed[4].

This figure differs from the calculation in the dossier by the pharmaceutical company, which assumes a total population of 6106 patients with cystic fibrosis. However, this figure is subject to uncertainties and represents an underestimate because patients lacking patient history data and up-to-date consent forms were not taken into account. Furthermore, there are currently no indications that the number of patients in the entire patient group has changed significantly since the 2012 Annual Report (8,042 patients registered at any time in the past while still alive. According to the information in the report, this figure has already been adjusted to eliminate duplicates).

1. The percentage of patients with confirmed homozygous *F508del* mutation in the CFTR gene is 46.75%[5] (3740 patients).
2. The percentage of patients between 2 and 5 years of age in the entire patient group is approx. 8.5% [4] (318 patients).
3. Taking into account that 87.24 % of patients are covered by statutory health insurance (SHI), there are 277 patients in the target population.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Orkambi® (active ingredient combination: lumacaftor/ivacaftor) at the following publicly accessible link (last access: 24 June 2019):

https://www.ema.europa.eu/documents/product-information/orkambi-epar-product-information_en.pdf

Treatment with lumacaftor/ivacaftor should only be initiated and monitored by specialists who are experienced in the treatment of patients with cystic fibrosis.

[4] https://www.muko.info/ (https://www.muko.info/englisch-version/) Website of Mukoviszidose e.V. (German Cystic Fibrosis Association) [accessed 27 June 2019]
[5] Nährlich L, Burkhart M, Wosniok J. German Cystic Fibrosis Registry: Berichtsband [Report volume] 2017 https://www.muko.info/fileadmin/user_upload/angebote/qualitaetsmanagement/register/berichtsband_2017.pdf.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 July 2019).

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy retail price level and also deducting the statutory rebates in accordance with Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the pharmaceutical costs were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
Medicinal product to be assessed				
Lumacaftor/ivacaftor	continuous, every 12 hours	365	1	365
Best supportive care	different for each individual patient			
Appropriate comparator therapy				
Best supportive care	different for each individual patient			

Usage and consumption:

Designation of the therapy	Dosage/ application	Dose/patient/treatment day	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Lumacaftor/ivacaftor	100 mg/ 125 mg	200 mg/ 250 mg	2 x 100 mg/125 mg	365	730 x 100 mg/125 mg
	or				
	150 mg/ 188 mg	300 mg/376 mg	2 x 150 mg/188 mg	365	730 x 150 mg/188 mg
Best supportive care	different for each individual patient				
Appropriate comparator therapy					

Designation of the therapy	Dosage/ application	Dose/patient/treatment day	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Best supportive care	different for each individual patient				

Costs:

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Lumacaftor/ivacaftor 100 mg/125 mg 150 mg/188 mg	56 granules in a sachet	€ 12,423.71	€ 1.77	€ 708.94	€ 11,713.00
Best supportive care	different for each individual patient				
Appropriate comparator therapy					
Best supportive care	different for each individual patient				

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 July 2019

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the usual expenditure in the course of the treatment are not shown.

No additionally required SHI services are taken into account for the cost representation.

3. Bureaucratic costs

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 29 January 2019.

On 8 February 2019, the pharmaceutical company submitted a dossier for the benefit assessment of lumacaftor/ivacaftor to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 11 February 2019 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient lumacaftor/ivacaftor.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 May 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 15 May 2019. The deadline for submitting written statements was 5 June 2019.

The oral hearing was held on 24 June 2019.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 6 August 2019, and the proposed resolution was approved.

At its session on 15 August 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	29 January 2019	Determination of the appropriate comparator therapy
Working group Section 35a	19 June 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	24 June 2019	Conduct of the oral hearing
Working group Section 35a	2 July 2019 16 July 2019 30 July 2019	Consultation on the dossier evaluation of the IQWiG and evaluation of the written statement procedure

Subcommittee Medicinal product	6 August 2019	Concluding discussion of the proposed resolution
Plenum	15 August 2019	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 August 2019

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The chair

Prof Hecken