Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Lumacaftor/ ivacaftor (reassessment after the deadline: cystic fibrosis, homozygous F508del mutation in CFTR gene, ≥ 2 to 5 years)

of 18 March 2022

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 the 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 decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The pharmaceutical company submitted a dossier for the early benefit assessment of the combination of active ingredients lumacaftor/ ivacaftor (Orkambi) to be assessed for the first time on 15 December 2015. For the resolution of 15 August 2019 made by the G-BA in this procedure, a limitation up to 1 October 2021 was imposed for the patient population of children aged 2 to 5 years with cystic fibrosis.

In accordance with Section 4, paragraph 3, No. 5 AM-NutzenV in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO, the procedure for the benefit assessment of the medicinal product Orkambi recommences when the deadline has expired.

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 5 VerfO on 28 September 2021.

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 3 January 2022, 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, 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 the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to 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 patients aged 2 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

Therapeutic indication of the resolution (resolution of 18 March 2022):

Orkambi granules are indicated for the treatment of cystic fibrosis (CF) in patients aged 2 to 5 years who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Children with cystic fibrosis aged 2 to 5 years who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

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 (in particular antibiotics for pulmonary infections, mucolytics, pancreatic

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

enzymes for pancreatic insufficiency, physiotherapy (as defined in the Remedies Directive), making full use of all possible dietary measures).

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 in accordance with 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 Federal Joint Committee has already determined the patient-relevant benefit 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 the symptomatic therapy of CF:

aztreonam[2], carbocisteine[3], ceftazidime, ciprofloxacin, colistimethate, dornase alfa[2], levofloxacin[4], Meronem, mannitol[4], pancreatin, tobramycin[2].

on 2. In the treatment of CF, nutritional measures, support of the respiratory function and physiotherapy (in the sense of the Remedies Directive) are basically considered as non-medicinal treatment.

on 3. No resolutions of the G-BA are available for the patient group "Children aged 2 years up to and including 5 years" to be considered in the present therapeutic indication.

The following resolutions of the G-BA on the early benefit assessment in elderly patients with cystic fibrosis who are homozygous for the F508del mutation in the CFTR gene are available:

- Tezacaftor/ ivacaftor: Resolution of 20 May 2021, children from 6 to < 12 years, additional benefit not proven

[2] Approved 6 years of age and above

[3] Currently not available

[4] Approved for adults only

- Ivacaftor: Resolution of 20 May 2021, children from 6 to < 12 years, additional benefit not proven
- Tezacaftor/ ivacaftor: Resolution of 17 December 2020, subjects aged 12 years and older, additional benefit not proven
- Ivacaftor: Resolution of 20 February 2020, subjects aged 12 years and older, additional benefit not proven
- Lumacaftor/ ivacaftor: Resolution of 2 August 2018, children aged 6 years to < 12 years, hint for a non-quantifiable additional benefit
- Lumacaftor/ ivacaftor: Resolution of 2 June 2016, subjects aged 12 years and older, indication of a considerable additional benefit

on 4. The generally accepted state of medical knowledge for the indication was established using a search for guidelines and systematic reviews of clinical studies. For patients aged 2 to 5 years with cystic fibrosis, there is no specific standard therapy according to the current state of medical knowledge. The above-mentioned medicinal and non-medicinal therapy options are available for symptomatic therapy. These are recommended in the present evidence for symptomatic therapy of CF, especially antibiotic therapy of pulmonary infections (ceftazidime, colistimethate, tobramycin), inhaled medicinal products (mannitol, dornase alfa), enzyme substitution for pancreatic insufficiency (pancreatin), nutritional therapy and support of respiratory function, physiotherapy. Thus, CF treatment is patient-individual in order to alleviate symptoms and improve quality of life in the sense of Best Supportive Care (BSC).

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:

<u>Children with cystic fibrosis aged 2 to 5 years who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.</u>

Hint for a non-quantifiable additional benefit

Justification:

The VX16-809-121 study (hereafter study 121) is used for the assessment of the additional benefit of LUM/ IVA in children with cystic fibrosis aged 2 to 5 years who are homozygous for the F508del mutation in the CFTR gene. Study 121 is a randomised, double-blind, 2-part study in which the first part compared LUM/ IVA + BSC with placebo + BSC. Following the 48-week double-blind treatment phase, all patients will be treated with LUM/ IVA for a further 48 weeks in the second part of the study.

The study included patients aged 2 to 5 years with cystic fibrosis who are homozygous for the F508del mutation in the CFTR gene. According to the inclusion criteria of the study, the

diagnosis of cystic fibrosis was defined by a sweat chloride concentration ≥ 60 mmol/l and a clinical manifestation. Patients who had an acute upper or lower respiratory tract infection or a pulmonary exacerbation were excluded. In addition, the basic medication for the treatment of cystic fibrosis should be kept stable within 28 days prior to the start of treatment.

A total of 51 patients were randomised in the study in a 2:1 ratio to either treatment with LUM/ IVA + BSC or placebo + BSC. The study was conducted exclusively in Germany.

The dosage of LUM/ IVA in the study 121 was as specified in the product information. In both study arms, an additional concomitant basic therapy was given.

The data presented in the dossier as well as from the data submitted in the written statement procedure clearly show that the children received comprehensive symptomatic therapy at the time of enrolment and during the study 121, including inhaled medication (saline, mucolytics, bronchodilators), antibiotics, digestive enzymes, vitamins and physiotherapy.

The data presented in the dossier and in the written statement procedure do not allow determination of whether adjustments to the concomitant treatment in the form of an increase in dose or frequency of symptomatic therapy were possible in the course of the study 121 and if so, the number of patients. Since it remains unclear whether the concomitant treatment used in the study 121 represents a full implementation of the appropriate comparator therapy BSC, uncertainties remain in this regard.

The primary endpoint of the study was the change in global chest score measured by magnetic resonance imaging (MRI). Furthermore, endpoints of the category of mortality, morbidity and side effects were assessed.

Furthermore, the non-randomised comparator cohort VX14-809-108 study (comparator cohort exclusive of subjects with heterozygous F508del mutation) and the single-arm VX16-809-116 study were additionally submitted by the pharmaceutical company in the dossier. In the written statement procedure, the pharmaceutical company also submitted the second part of the study 121 (single-arm, 96-week data). The VX14-809-108 and VX16-809-116 studies as well as the single-arm extension study 121 are not considered for the present benefit assessment due to the absence of a control group compared with the appropriate comparator therapy.

Extent and probability of the additional benefit

Mortality

There were no deaths in the 121 study.

Morbidity

Pulmonary exacerbations and hospitalisation due to pulmonary exacerbations

Pulmonary exacerbations, especially those leading to hospitalisation, are a clinically relevant endpoint and should be considered patient-relevant.

For the endpoints of pulmonary exacerbations and hospitalisation due to pulmonary exacerbations, there was no statistically significant difference between the treatment groups in the study 121.

Body Mass Index (BMI) and BMI z-score

BMI is used to assess body weight in relation to height. The body weight or BMI is important in the present indication because developmental disorders and impaired nutrient absorption are among the typical signs of cystic fibrosis. This endpoint is assessed as a patient-relevant morbidity parameter, especially in children with characteristic, disease-related growth disorders. Data adjusted for age and sex (z-scores) are preferred over absolute values.

The study 121 shows a statistically significant difference in the BMI z-score to the advantage of LUM/ IVA + BSC compared to placebo + BSC, the extent of which cannot be conclusively assessed.

Sweat chloride concentration (mmol/l)

The determination of the sweat chloride concentration is used as standard in the diagnostic process as the values reflect the functionality of the CFTR protein, which is the pathophysiological cause of the disease. The endpoint is not considered directly patient-relevant and is considered additionally as the extent of a reduction in sweat chloride concentration is not directly associated with the extent of change in symptomatology.

The endpoint of sweat chloride concentration was surveyed in the study 121 as absolute change during week 48. There is a statistically significant difference to the advantage of LUM/ IVA + BSC compared to placebo + BSC in terms of the absolute change in sweat chloride concentration.

Lung Clearance Index ($LCI_{2,5}$)

The Lung Clearance Index is a measure for assessing the ventilation inhomogeneity of the lungs and is measured using the gas washout test. The study measured the absolute change in $LCI_{2,5}$ after 24 weeks of treatment compared to the start of the study.

The $LCI_{2,5}$ is considered a surrogate endpoint. Based on the studies submitted by the pharmaceutical company, it cannot be concluded that the $LCI_{2,5}$ is a valid surrogate parameter for patient-relevant endpoints. However, an influence on the course of the disease can only be measured to a very limited extent in the very young patient population under consideration here, which still has relatively few symptoms. In the written statement procedure, it became clear that the $LCI_{2,5}$ endpoint for detecting early changes in cystic fibrosis is established in clinical practice in this therapeutic indication. Against this background, $LCI_{2,5}$ is used as the relevant endpoint in the age group of patients with cystic fibrosis to be considered here for the benefit assessment. However, due to the lack of long-term data for the $LCI_{2,5}$, the

significance of the results with regard to longer-term effects, such as pulmonary exacerbations and improvement of symptomatology, is limited.

No statistically significant difference was found for $LCI_{2,5}$ between the treatment groups.

MRI score

MRI scores are used by default for follow-up in clinical practice in the present indication in 2-5-year-old children.

The endpoint is not considered directly patient-relevant and is considered additionally as a change in the MRI score is not directly associated with the extent of change in symptomatology.

For the MRI Global Chest Score, MRI Morphological Chest Score and MRI Perfusion Chest Score, no statistically significant difference was observed between the treatment groups in the study 121.

Quality of life

Endpoints on health-related quality of life were not assessed in the study 121.

Side effects

For the endpoint of discontinuation due to AEs, no event occurred in the study 121. This does not result in any difference between the treatment groups.

For the endpoint of SAEs, no statistically significant difference was detected between the treatment groups.

In the side effects category, the overall analysis did not show any statistically significant difference between the treatment arms.

Overall assessment

The randomised, double-blind, placebo-controlled phase III study 121 was used for the new benefit assessment after the expiry of LUM/ IVA for the treatment of children with cystic fibrosis aged 2 to 5 years who are homozygous for the F508del mutation in the CFTR gene. This study yielded results on mortality, morbidity and side effects.

There were no deaths in the 121 study.

There are no statistically significant differences between the treatment arms for the endpoints of pulmonary exacerbations, hospitalisation due to pulmonary exacerbations and $LCI_{2,5}$ and for the endpoint of MRI score presented additionally.

In the endpoint of BMI z-score, there is a statistically significant difference to the advantage of LUM/ IVA + BSC compared to placebo + BSC, the extent of which cannot be conclusively

assessed. In the endpoint of sweat chloride concentration presented additionally, a statistically significant advantage of LUM/ IVA + BSC over placebo + BSC was found.

Endpoints on health-related quality of life were not assessed in the study 121.

In the side effects category, the overall analysis did not show any statistically significant difference between the treatment arms.

Cystic fibrosis is a progressive disease, i.e. the manifestation increases with age, so that younger patients with cystic fibrosis - such as the children under consideration here - still show relatively few symptoms. This means that an influence of the course of the disease on patient-relevant endpoints can only be measured to a limited extent. Thus, symptom burden and improvement of symptoms in the LUM/ IVA arm is more evident in patients aged 12 years and older compared to children aged 2 to 5 years.

For children aged ≥ 6 to < 12 years, LUM/ IVA showed an advantage over BSC for the endpoint $LCI_{2,5}$ which is used to detect early changes in cystic fibrosis due to its clinical significance.

Advantages of LUM/ IVA over BSC were found in older children and adolescents aged 12 years and older in the present therapeutic indication. These include the patient-relevant endpoints BMI or BMI z-score and pulmonary exacerbations.

The additional benefit identified in the populations ≥ 6 to < 12 years (resolution of 02.08.2018) and ≥ 12 years (resolution of 02.06.2016) is taken into account in the overall assessment, considering the advantage in the BMI and BMI z-score respectively in children aged 2 to 5 years and children and adolescents aged 12 years and older, and the advantages of LUM/ IVA in the older patients ≥ 6 to < 12 years and ≥ 12 years in the above endpoints, and given the fact that there is an identical underlying genetic cause of the disease and a comparable pathophysiology, that the severity of symptoms only increases with age, and in view of the identical appropriate comparator therapies in the three populations. However, the extent is non-quantifiable due to the associated uncertainties and limitations of the available evidence.

Conclusion

Taken together, an additional benefit of LUM/ IVA compared with the appropriate comparator therapy, the extent of which cannot be quantified due to the limited evidence available, can be identified in the treatment of cystic fibrosis in children aged 2 to 5 years who are homozygous for the F508del mutation in the CFTR gene based on the results of the study 121, and taking into account the results of the VX14-809-109 study in children aged ≥ 6 to < 12 years and the results of the VX12-809-103 and VX12-809-104 studies in children and adolescents aged 12 years and older.

Reliability of data (probability of additional benefit)

This assessment is based on the results of the study 121 in children aged 2-5 years, taking into account the assessment of LUM/ IVA in children aged ≥ 6 to < 12 years and in children and adolescents aged 12 years and older.

An overall hint is derived due to the limitations of the available evidence as well as the uncertainties of patient-relevant effects in this age group.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of the medicinal product Orkambi® with the active ingredient lumacaftor/ ivacaftor (LUM/IVA) after expiry of the deadline. LUM/ IVA is indicated for the treatment of cystic fibrosis (CF) in children aged 2 to 5 years and older who are homozygous for the F508del mutation in the CFTR gene.

The G-BA determined Best Supportive Care (BSC) to be the appropriate comparator therapy.

The randomised, double-blind, placebo-controlled phase III study 121 was used for the benefit assessment of LUM/ IVA.

There were no deaths in the 121 study.

There are no statistically significant differences between the treatment arms for the endpoints of pulmonary exacerbations, hospitalisation due to pulmonary exacerbations and $LCI_{2,5}$.

In the endpoint of BMI z-score, there is a statistically significant difference to the advantage of LUM/ IVA + BSC compared to placebo + BSC, the extent of which cannot be conclusively assessed.

Endpoints on health-related quality of life were not assessed in the study 121.

In the side effects category, the overall analysis did not show any statistically significant difference between the treatment arms.

The VX14-809-108 and VX16-809-116 studies additionally submitted by the pharmaceutical company as well as the single-arm extension study 121 are not considered for the present benefit assessment due to the absence of a control group compared with the appropriate comparator therapy.

Taken together, an additional benefit of LUM/ IVA compared with the appropriate comparator therapy, the extent of which cannot be quantified due to the limited evidence available, can be identified in the treatment of cystic fibrosis in children aged 2 to 5 years who are homozygous for the F508del mutation in the CFTR gene based on the results of the study 121, and taking into account the results of the VX14-809-109 study in children aged ≥ 6 to < 12 years and the results of the VX12-809-103 and VX12-809-104 studies in children and adolescents aged 12 years and older. A hint for a non-quantifiable additional benefit can be identified due to the associated uncertainties and the limitations of the available evidence.

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

In order to ensure consistent consideration of the patient numbers taking into account the most recent resolution (19 November 2021) on the benefit assessment of medicinal products

with new active ingredients according to Section 35a SGB V in the therapeutic indication of cystic fibrosis, the G-BA uses the following derivation of the patient numbers:

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

Altogether, it is assumed that there are currently about 8,000 patients with cystic fibrosis in Germany[5].

This amount differs from the calculation of the pharmaceutical company in the dossier, which assumes 6,340 patients with cystic fibrosis in the total population. However, this figure is subject to uncertainties and is underestimated, as those patients without process data and without a current informed consent form were not taken into account here. In addition, there is currently no evidence that the overall patient population has changed meaningfully since the 2012 reporting volume (8,042 patients ever reported and alive at the time. This figure has already been adjusted for multiple responses according to the information in the report volume).

1. The percentage of patients with confirmed homozygous F508del mutation in the CFTR gene is 45.81%[6] (3,665 patients).
2. The percentage of patients between 2 and 5 years of age in the total collective is about 9%[6] (330 patients).
3. Taking into account a percentage of SHI-insured patients of 88.08%, this results in 291 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: lumacaftor/ ivacaftor) at the following publicly accessible link (last access: 2 February 2022):

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

Treatment with lumacaftor/ ivacaftor should only be initiated and monitored by doctors experienced in the therapy of children with cystic fibrosis.

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: 1 March 2022).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number

[5] Mukoviszidose e.V. - Federal Association for Cystic Fibrosis (CF) Website Mukoviszidose e.V.

[6] Nährlich L, Burkhart M, Wosniok J. German Mucoviscidosis Registry, Report Volume 2019. 2020.

of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

For dosage depending on body weight, the average body measurements from the official representative statistics “Microcensus 2017 – body measurements of the population” were applied. The average body weight of 2-year-olds is 14.1 kg and that of 5-year-olds 20.8 kg.[7]

The dosage of lumacaftor/ ivacaftor recommended for children varies depending on body weight. According to the product information, children with a body weight of 14 kg and above receive 150 mg/188 mg lumacaftor/ ivacaftor 2 x daily.

Since the best supportive care treatment of cystic fibrosis is patient-individual, no specific costs for the appropriate comparator therapy can be mentioned here. In addition, best supportive care treatment is provided both within the scope of the lumacaftor/ ivacaftor medicinal product to be assessed and within the scope of the appropriate comparator therapy.

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	Continuously, 2 x daily	365	1	365
Best supportive care	Different from patient to patient			
Appropriate comparator therapy				
Best supportive care	Different from patient to patient			

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					

[7] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Lumacaftor/ ivacaftor	150 mg/ 188 mg	300 mg / 366 mg	2 x 150 mg/ 188 mg	365	730 x 150 mg/ 188 mg
Best supportive care	Different from patient to patient				
Appropriate comparator therapy					
Best supportive care	Different from patient to patient				

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 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 costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging 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 150 mg / Ivacaftor 188 mg	56 GRA	€ 12,423.71	€ 1.77	€ 708.94	€ 11,713.00
Best supportive care	Different from patient to patient				
Appropriate comparator therapy					
Best supportive care	Different from patient to patient				
Abbreviations: GRA = granules					

LAUER-TAXE® last revised: 1 March 2022

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 standard expenditure in the course of the treatment are not shown.

Because there are no 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, no costs for additionally required SHI services had to be taken into account.

3. Bureaucratic costs calculation

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

At its session on 29 January 2018, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 28 September 2021, 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 5 VerfO.

By letter dated 29 September 2021 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 23 December 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 3 January 2022. The deadline for submitting written statements was 24 January 2022.

The oral hearing was held on 7 February 2022.

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 was discussed at the session of the subcommittee on 9 March 2022, and the proposed resolution was approved.

At its session on 18 March 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	29 January 2018	Determination of the appropriate comparator therapy
Working group Section 35a	1 February 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	7 February 2022	Conduct of the oral hearing
Working group Section 35a	15 February 2022 1 March 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	9 March 2022	Concluding discussion of the draft resolution
Plenum	18 March 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 18 March 2022

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

Prof. Hecken