Gemeinsamer Bundesausschuss

Justification

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII - Annex XII - Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Ivacaftor (new therapeutic indication: cystic fibrosis, patients from 4 < 6 months, gating mutations)

of 20 May 2021

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:

1st Approved therapeutic indications,

2nd Medical benefit,

3rd Additional medical benefit in relation to the appropriate comparator therapy,

4th Number of patients and patient groups for whom there is a therapeutically significant additional benefit,

5th Treatment costs for statutory health insurance funds,

6th 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 active ingredient ivacaftor (kalydeco) was listed for the first time on 15 August 2012 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

Within the previously approved therapeutic indications, the sales volume of ivacaftor with the statutory health insurance at pharmacy retail prices including value-added tax exceeded € 50 million. Proof must therefore be provided for ivacaftor in accordance with Section 5, paragraph 1 through 6 VerfO, and the additional benefit compared with the appropriate comparator therapy must be demonstrated.

On 3 November 2020, kalydeco received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2a letter a to Regulation (EC) No. 1234/2008 of the commission of 24 November 2008 concerning the examination of amendments 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 24 November 2020, i.e. at the latest within four weeks after the disclosure of the pharmaceutical company on the approval of a new area of application, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 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 G-BA on the active ingredient ivacaftor with the new therapeutic indication (cystic fibrosis, patients from 4 < 6 months with gating mutations).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 March 2021 on the G-BA website (www.g-ba.de), 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 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, and the addenda to the benefit assessment prepared by the IQWiG. 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 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 ivacaftor (kalydeco) in accordance with the product information

Kalydeco granules are indicated for the treatment of infants aged at least 4 months, toddlers and children weighing between 5 kg to less than 25 kg with cystic fibrosis (CF) who have an *R117H CFTR*-Mutation or one of the following gating (class III) mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N* or *S549R*.

Therapeutic indication of the resolution (resolution of 20 May 2021):

Kalydeco granules are indicated for the treatment of infants aged at least 4 < 6 months who have one of the following gating mutations (class III) in the *CFTR* gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

[1] General Methods, version 6.0 of 5.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Infants with cystic fibrosis aged at least 4 to < 6 months who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R

Appropriate comparator therapy for ivacaftor:

- Best supportive care

Best Supportive Care (BSC) is defined as the therapy that ensures the best possible, patient-individually optimised, supportive treatment to alleviate symptoms and improve the quality of life (in particular antibiotics for pulmonary infections, mucolytics, pancreatic 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 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 the symptomatic therapy of CF: aztreonam[2]carbocisteine[3], ceftazidime, ciprofloxacin, colistimethate, dornase alfa[2], levofloxacin[4], meronem, mannitol[4], pancreatin, tobramycin[2].

zu 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-drug treatment.

[2] approved from 6 years
[3] currently not available
[4] only approved for adults

On 3. For the patient group to be considered in the field of application *"Infants with cystic fibrosis aged at least 4 < 6 months who have one of the following gating (class III) mutations in the CFTR gene*: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R"* there are no resolutions.

The following decisions of the G-BA on the early benefit assessment in elderly patients with cystic fibrosis who have one of the above-mentioned gating mutations are available:

- Ivacaftor: Resolution of 4 June 2020, patients 6 < 12 months of age, hint of unquantifiable additional benefit,
- Ivacaftor: Resolution of 20 February 2020, patients aged 12 < 24 months, hint of unquantifiable additional benefit,
- Ivacaftor: Resolution of 20 February 2020, patients aged 2 to 5 years, evidence of unquantifiable additional benefit,
- Ivacaftor: Resolution of 20 February 2020, patients 6 to 11 years of age and older with G551D mutation, evidence of unquantifiable additional benefit; patients 12 years of age and older with G551D-Mutation, evidence of substantial additional benefit,
- Ivacaftor: Resolution of 20 February 2020, patients 6 years and older with gating mutations (not G551D), evidence of substantial additional benefit.

On 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. For patients with cystic fibrosis aged 4 < 6 months, there is no specific standard therapy according to the current state of medical knowledge. The above-mentioned medicinal and non-drug 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 (ceftazidine, colistimethate, tobramycin), inhalation of medicinal products (mannitol, dornase alfa), enzyme substitution for pancreatic insufficiency (pancreatin), nutritional therapy and support of respiratory function and physiotherapy. In CF, treatment is thus 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 order.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of ivacaftor is assessed as follows:

<u>Infants with cystic fibrosis aged at least 4 to < 6 months who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R</u>

Hint of non-quantifiable additional benefit

Justification:

For the evaluation of the additional benefit of ivacaftor after new therapeutic indication for the treatment of infants with cystic fibrosis aged at least 4 < 6 months who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R, the pharmaceutical company submits the single-arm, open-label Phase III registration study VX15-770-124 (hereafter 124). In the present indication in elderly patients from 6 < 12 months of age[5] or from 12 < 24 months[6] the study 124 has already been assessed.

In addition, due to a lack of comparative data, the pharmaceutical company refers to the results of three previously evaluated studies on ivacaftor in elderly patients with cystic fibrosis and one of the above-mentioned gating mutations. On the one hand, the pharmaceutical company draws on studies VX08-770-103 (hereafter 103) and VX08-770-102 (hereafter 102), each in children 6 to 11 years of age and older patients 12 years of age and older with a G551D mutation[7]and the VX12-770-111 study (hereafter 111) in patients aged 6 years and older with one of the above-mentioned gating mutations (not G551D)[8]. Here, the pharmaceutical company assumes transferability of these data to the patient group of infants aged 4 < 6 months to be considered here.

124 study

The single-arm, open-label Study 124 is divided into two phases (Parts A and B) and evaluates treatment with ivacaftor in infants and young children up to less than 24 months of age with cystic fibrosis and gating mutations. While in part A the ivacaftor treatment lasted 4 days, in part B it lasted 24 weeks. For the early benefit assessment, the pharmaceutical company only considers Part B in the appropriately relevant Cohort 7, in which a total of 6 infants aged at least 4 < 6 months were included. A G551D mutation was present in 5 infants. At the time of screening, included patients had to have a bodyweight of at least 5 kg. Treatment with ivacaftor was in addition to concomitant therapy for cystic fibrosis. From the data presented in the dossier, it appears that patients received comprehensive symptomatic concomitant therapy at study entry and throughout the course of the study. For the early benefit assessment, only part B of study 124 is considered.

The primary endpoint of Study 124 in Part B was safety and tolerability data such as adverse events. In addition, sweat chloride measurements were performed, and pulmonary exacerbations, weight and height were recorded.

Results of study 124 (cohort 7)

Mortality

In Study 124, no deaths occurred in infants 4 < 6 months of age treated with ivacaftor.

[5] Benefit assessment resolution for ivacaftor (patients ≥ 6 < 12 months with various gating mutations) https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/514/#beschluesse

[6] Benefit assessment procedure for ivacaftor (patients ≥ 12 < 24 months with various gating mutations) https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/486/#beschluesse

[7] Benefit assessment procedure for ivacaftor (patients ≥ 6 years with G551D-Mutation) https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/431/#beschluesse

[8] Benefit assessment procedure for the active substance ivacaftor (patients with various gating mutations (not G551D) ≥ 6 years) https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/483/#beschluesse

Morbidity

Pulmonary exacerbations and hospitalisations for pulmonary exacerbations

Pulmonary exacerbations, especially those leading to hospitalisation, represent a clinically relevant endpoint and are considered patient-relevant. Two different definitions of pulmonary exacerbations were used in Study 124. Even when both definitions are included, the frequency of pulmonary exacerbations in this age group is very low. The same applies to hospitalisations due to pulmonary exacerbations.

Ratio of body weight to height - z-scores

In study 124, the change in z-score from bodyweight to height over 24 weeks was collected as an endpoint. The ratio of body weight to body size is important for the present indication, since developmental disorders and impaired nutrient absorption are among the typical signs of cystic fibrosis. This endpoint is considered to be a patient-relevant morbidity parameter, especially in children and infants with characteristic, disease-related growth disorders. Data adjusted for age and sex (z-scores) are preferred over absolute values.

The included infants already had a bodyweight to height ratio at baseline that was within the normal range for the healthy population of the same age and sex (z-score). At the end of the study, there were no changes in the body weight to height ratio at baseline. However, it cannot be conclusively assessed to what extent the increasing age and development of the patients influences the outcome.

Sweat chloride concentration

The measurement of chloride levels in sweat is used as a standard diagnostic procedure, as the values reflect the functionality of the CFTR protein, which is the pathophysiological cause of the disease. Because the magnitude of a reduction in sweat chloride concentration is not directly associated with the magnitude of change in symptomatology, the endpoint is not considered directly relevant to the patient and is considered supplemental.

Study 124 showed a significant reduction in sweat chloride levels after 24 weeks compared to baseline.

Quality of life

Endpoints in the health-related quality of life category were not examined in Study 124.

Side effects

Adverse events occurred in all infants, and serious adverse events were suffered by one patient (16.7%). No patient discontinued treatment with ivacaftor due to adverse events.

Evaluation with regard to transfer of additional benefit

Although the above-described study 124 is not suitable for the assessment of the additional benefit compared to the appropriate comparator therapy due to its single-arm design, it provides supporting data for a transfer of the additional benefit.

The European Medicines Agency (EMA) 2020 assessment report[9] states that the uncontrolled study 124 was used as the basis for extrapolating efficacy data from previously approved patient groups (adults, adolescents, children 6 years and older, and 2 years and older,

[9] Assessment Report; EMEA/H/C/002494/II/0086 dated 17 September 2020; available from: https://www.ema.europa.eu/en/documents/variation-report/kalydeco-h-c-2494-ii-0086-epar-assessment-report-variation_en.pdf *[Accessed 22/4/2021]*

respectively) to infants 4 < 6 months of age with the gating mutations G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R.

The EMA's findings on the medical rationale for transferring data from older patient groups to infants aged 4 < 6 months in the same therapeutic area are also decisive for the G-BA for an evidence transfer.

Cystic fibrosis is an inherited multisystem disease in which mutations in the CFTR gene cause disruptions in the chloride channel of exocrine glands. The pathophysiological background (disturbance in the chloride channel) is thus identical for the patient group of 4 < 6 months old infants relevant here with that of older patients. Treatment with ivacaftor modulates the functionality of the chloride channels, regardless of the age of the patient.

The course of cystic fibrosis is progressive, i.e. the manifestation becomes stronger with increasing age, so that younger patients with cystic fibrosis still show relatively few symptoms.

The lower symptom burden and improvement in symptoms in the ivacaftor arm is also evident in patients aged 6 to 11 years compared to older patients aged 12 years and older. Both age groups were investigated in studies 103 and 102 in patients with a G551D-Mutation and support this fact[7].

The appropriate comparative therapy defined by the G-BA for patients with cystic fibrosis with a gating mutation is identical for infants from 4 < 6 months of age as well as for older patients from 6 or 12 years of age (best supportive care). In this respect, a decisive criterion for evidence transfer in the context of the early benefit assessment is given. The standards to be applied for the acceptance of evidence-based on a low degree of evidence will also take into account the specificities and limitations of the conduct of paediatric clinical studies.

Considering the fact that there is an identical underlying genetic cause of the disease with comparable pathophysiology, and taking into account the presented data of study 124 in infants from 4 < 6 months of age with predominant G551D-Mutation, which indicate largely similar effects in efficacy compared to the already assessed studies 103 and 102 in patients 6 years of age and 12 years of age and older with G551D mutation, respectively, as well as considering the identical appropriate comparator therapy, it is assumed that the positive effects of ivacaftor are transferable. In particular, the advantage of ivacaftor on the endpoint "BMI z-score" is considered.

The G551D-Mutation represents the most common gating mutation in the CFTR gene. The presence of this mutation was an inclusion criterion for the aforementioned studies 103 and 102, which demonstrated an additional benefit of ivacaftor compared to the appropriate comparator therapy. Therefore, a hint of non-quantifiable additional benefit was derived for children aged 6 to 11 years and an indication of substantial additional benefit was derived for older patients aged 12 years and older[7].

The effects of ivacaftor treatment in patients 6 years of age and older with one of the above gating mutations (non-G551D) was again investigated in the 8-week randomised, placebo-controlled cross-over study 111[8]. Compared to BSC, there were advantages in the endpoint FEV_1 as well as in the domains vitality and subjective health assessment of the questionnaire CFQ-R in patients aged 14 years and older. An advantage of ivacaftor over BSC was also shown for the endpoint BMI z-score, although the relevance of the extent could not be conclusively assessed, as values in the normal range were already present in both treatment groups at baseline. As the 8-week study duration was too short to assess the sustainability of patient-

relevant endpoints, the findings of the regulatory authority EMA[10] were taken into account, in which a sufficient concordance of the data between week 8 in study 111 and week 24 in studies 102 and 103 was assumed. Overall, a hint or an unquantifiable additional benefit of ivacaftor over BSC was established in this patient group[8].

In view of the positive effects observed in patients with a G551D-Mutation[7] and assuming that comparable effects are achieved by ivacaftor treatment in patients with a G551D-Mutation as well as in patients with various gating mutations (not G551D)[8], in the evaluation of infants aged 4 < 6 months to be considered here, the established additional benefit of ivacaftor in the treatment of older patients, in particular those over 12 years of age with a G551D-Mutation[7] and additionally children aged 6 years and older each with a G551D-Mutation[7] or with various gating mutations (not G551D)[8], is considered.

The derived transferability of the additional benefit is appropriate on the basis of the previously presented argumentation to younger patients, in the present benefit assessment to 4 < 6 months old infants - with cystic fibrosis and the same gating mutations.

Conclusion

Overall, the G-BA concludes that the transferability of the additional benefit to ivacaftor from children and adolescents aged 6 and 12 years and older is assumed to infants aged 4 to 6 months with cystic fibrosis with the following gating mutations: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R, particularly in light of the comparable clinical picture, progressive course, and limitations in conducting clinical studies in this age group. However, the additional benefit cannot be quantified, as the scientific data situation does not allow this at the present time.

Reliability of data (probability of additional benefit)

Due to the uncertainty caused by the transfer of the additional benefit to a younger population, a hint of a non-quantifiable additional benefit can be identified.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient ivacaftor (Kalydeco®). The therapeutic indication evaluated here includes infants with cystic fibrosis aged 4 < 6 months who have one of the following gating mutations (class III) in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R.

Kalydeco® was approved as an orphan drug, but has exceeded the EUR 50 million turnover limit.

The appropriate comparator therapy of Best Supportive Care was determined as follows by the G-BA.

For the benefit assessment, the pharmaceutical company submits the single-arm, open-label phase III study VX15-770-124. Although the study is not suitable for the assessment of additional benefit compared to the appropriate comparator therapy due to its single-arm design, it provides supporting data for a transfer of additional benefit.

[10] Assessment Report; EMEA/H/C/002494/II/0009 dated 26 June 2014; available from: https://www.ema.europa.eu/en/documents/variation-report/kalydeco-h-c-2494-ii-0009-epar-assessment-report-variation_en.pdf

Due to a lack of comparative data, the results of studies with ivacaftor in elderly patients were used. Based on these studies, a hint of unquantifiable additional benefit was derived in both 6- to 11-year-old children with G551D-Mutation[7] and patients 6 years and older with other gating mutations (non-G551D)[8], and a hint of substantial additional benefit was derived in patients 12 years and older with G551D-Mutation[7], both compared with BSC.

Particularly against the background of the comparable clinical picture, the progressive course and the limitations in the conduct of clinical studies, the G-BA concludes that the transferability of the additional benefit of ivacaftor from the older patients aged 6 or 12 years and older to the 4- < 6-month-old infants to be considered here is assumed. Due to the uncertainty caused by the transfer of the additional benefit to a younger population, a hint of non-quantifiable additional benefit can be identified.

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

In order to ensure a consistent consideration of the patient numbers taking into account the most recent resolution (18 February 2021) on the benefit assessment of drugs with new active ingredients according to Section 35a SGB V in the therapeutic area 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[11].

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 follow-up 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).

However, the number of 1 patient in the SHI target population calculated by the pharmaceutical company is consistent with IQWIG's own calculations using the proportion values for the mutations determined by the pharmaceutical company and the associated uncertainties. The number of 1 patient in the SHI target population thus seems plausible.

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 Kalydeco (active ingredient: ivacaftor) at the following publicly accessible link (last access: 1 April 2021):

[11] https://www.muko.info/ Mukoviszidose e.V. website. [Accessed 27 Jun. 2019]

https://www.ema.europa.eu/documents/product-information/kalydeco-epar-product-information_de.pdf

Treatment with ivacaftor should only be initiated and monitored by specialists who are experienced in the treatment of patients 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 May 2021).

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 Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular strength was first determined on the basis of consumption. Having determined the number of packs of a particular strength, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

For the calculation of the dosages, the dosage recommendations of the expert information are decisive. Accordingly, infants aged 4 months < 6 months are assumed to have a bodyweight of at least 5 kg (≥ 5 kg < 7 kg). In this patient, a single dose of 25 mg ivacaftor granules every 12 hours is recommended. Accordingly, a total daily dose of 50 mg is used.

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.

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

Patients in the present application area receive best supportive care. The treatment costs for best supportive care are different for each individual patient.

Because best supportive care has been determined as an appropriate comparator therapy, this is also reflected in the medicinal product to be assessed.

The type and scope of best supportive care can vary depending on the medicinal product to be assessed and the comparator therapy.

Treatment duration:

Name of therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Days of treatment/patient/ Year
Medicinal product to be assessed				
Ivacaftor	continuously,	365	1	365

Name of therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Days of treatment/patient/ Year
	twice daily			
Best supportive care	Patient-individual			
Appropriate comparator therapy				
Best supportive care	Patient-individual			

Consumption:

Name of therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by strength/day of treatment	Days of treatment/ patient/ Year	Average annual consumption by strength
Medicinal product to be assessed					
Ivacaftor	25 mg	50 mg	twice 25 mg	365	730 x 25 mg
Best supportive care	Patient-individual				
Appropriate comparator therapy					
Best supportive care	Patient-individual				

Costs:

Costs of the medicinal product:

Name of 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					

Name of therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Ivacaftor 25 mg	56 GRA	€ 16,432.12	€ 1.77	€ 937.86	€ 15,492.49
Best supportive care	Patient-individual				
Appropriate comparator therapy					
Best supportive care	Patient-individual				
Abbreviations: GRA = Granules in a bag					

LAUER-TAXE® last revised: 1 May 2021

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 cost 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

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 10 November 2020.

On 24 November 2020, the pharmaceutical company submitted a dossier for the benefit assessment of ivacaftor to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 26 November 2020 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 ivacaftor.

The dossier assessment by the IQWiG was submitted to the G-BA on 25 February 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 1 March 2021. The deadline for submitting written statement procedures was 22 March 2021.

The oral hearing was held on 6 April 2021.

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 11 May 2021, and the draft resolution was approved.

At its session on 20 May 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	10 November 2020	Determination of the appropriate comparator therapy
Working group Section 35a	31 March 2021	Information on written statement procedures received; preparation of the oral hearing
Subcommittee Medicinal products	6 April 2021	Conduct of the oral hearing
Working group Section 35a	14 April 2021 5 May 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	11 May 2021	Concluding consultation of the draft resolution
Plenum	20 May 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 20 May 2021

Federal Joint Committee in accordance with Section 91 SGB V The chairman

Prof. Hecken