Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Ivacaftor (Exceeding the € 50 Million Limit: Cystic Fibrosis, Patients from 2 to 5 years)

of 20 February 2020

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 decides 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 ivacaftor (Kalydeco®) was listed for the first time on 23 July 2012 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices. Kalydeco® for the treatment of cystic fibrosis is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999.

In its session on 2 June 2016, the G-BA passed a resolution on the benefit assessment of ivacaftor in the therapeutic indication "Treatment of children from 2 to 5 years of age with cystic fibrosis who have one of the following gating mutations (class III) in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R" in accordance with Section 35a SGB V.

If the turnover of the orphan drugs with statutory health insurance at pharmacy sales prices as well as outside statutory medical care, including value added tax, exceeds € 50 million in the last twelve calendar months, the pharmaceutical company must, within three months of being requested to do so by the Federal Joint Committee, submit evidence in accordance with Section 5, paragraph 1 through 6 demonstrating the additional benefit compared with the appropriate comparator therapy.

The pharmaceutical company was informed about the exceeding of the € 50 million turnover limit by letter dated 22 March 2019 and was requested to submit a dossier for the benefit assessment in accordance with 35a SGB V. The pharmaceutical company submitted the final dossier to the G-BA in due time 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 6 VerfO on 28 August 2019.

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 2 December 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 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 ivacaftor.

In the light of the above and taking into account the statements 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 ivacaftor (Kalydeco®) in accordance with the product information (April 2019)

Ivacaftor is indicated for the treatment of children aged 12 months and older and a body weight between 7 and 25 kg with cystic fibrosis (CF) who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R.

This resolution concerns only the therapeutic indication for children aged 2 to 5 years with cystic fibrosis with one of the following gating (class III) mutations 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:

Children aged 2 to 5 years with cystic fibrosis who have one of the following gating (class III) mutations in the CFTR gene G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R:

- 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

[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.

insufficiency, physiotherapy (in the sense of the Heilmittel-RL (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 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:

On 1. The following medicinal products are approved for symptomatic therapy of CF: Aztreonam[2] (Cayston®), carbocisteine[3], ceftazidim, ciprofloxacin, colistimethate, dornase alfa[2] (Pulmozyme®), levofloxacin[4], meronem, mannitol[4] (Bronchitol®), 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 generally considered as non-medicinal treatment.

On 3. For the patient group to be considered in the present therapeutic indication “children aged 2 to 5 years with cystic fibrosis who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G5515, S1251N, S1255P, S549N, or S549R , the G-BA has passed the following resolution:
   - Resolution on ivacaftor dated 2 June 2016 (*Orphan Drug* Status; is repealed with the present resolution)

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 aged 2 to 5 years with cystic fibrosis, there is no specific standard therapy according to the current state of medical knowledge. 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, dornase alfa), enzyme substitution for pancreatic insufficiency (pancreatin), and nutritional therapy and support of respiratory function (e.g. through physiotherapy). CF is thus treated

[2] approved for 6 years and older
[3] approved for 13 years and older
[4] approved only for adults

individually for each patient to alleviate symptoms and improve the 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 contract.

2.1.3 Extent and probability of the additional benefit

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

For the treatment of children aged 2 to 5 years with cystic fibrosis 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 is a hint for a non-quantifiable additional benefit.

Justification:

For the benefit assessment of ivacaftor in children aged 2 to 5 years with cystic fibrosis who have one of the aforementioned gating mutations (class III) in the CFTR gene, the pharmaceutical company presents a single-arm study (VX11-770-108, hereinafter referred to as 108) and its expansion study (VX11-770-109, hereinafter referred to as 109). An eight-week randomised placebo-controlled cross-over study (VX15-770-123) was not used for the benefit assessment because it was stopped early because of insufficient recruitment of patients after marketing authorisation of the medicinal product and is therefore not suitable because of the lack of interpretability of the results. Because of the lack of comparative data, the pharmaceutical company has transferred the results of ivacaftor treatment in children aged 6–11 years with a G551D mutation (Study VX08-770-103, hereinafter Study 103) and in patients ≥ 12 years (Study VX08-770-102, hereinafter Study 102) to the target population of children aged 2–5 years. Furthermore, the pharmaceutical company uses the results of the Study VX12-770-111 (hereinafter Study 111, from 6 years of age) for ivacaftor treatment in the presence of a non-G551D gating mutation.

Study 108 of 2- to 5-year-old children with cystic fibrosis is a single-arm, open-label Phase III study. All patients in Study 108 received ivacaftor. Study 108 is divided into two phases. In Part A (n = 9) the patients received ivacaftor over a period of 4 days. The treatment duration in Part B (n = 34) was 24 weeks. Only Part B of Study 108 is considered for the present benefit assessment. The dosage of ivacaftor was weight adapted according to the product information.

Study 108 included patients aged 2 to 5 years with confirmed diagnosis of cystic fibrosis (sweat chloride value ≥ 60 mmol/l or two mutations in the CFTR gene) and one of the following mutations in the CFTR gene: G551D, G178R S549N, S549R G551S, G970R, G1244E, S1251N, S1255P, G1349D. The patients included had to have a body weight of ≥ 8 kg at the time of the screening. Patients with severely limited liver function, acute respiratory infection, or pulmonary exacerbations were excluded from the study population.

From the data presented in the dossier, it is clear that the patients received comprehensive symptomatic medicinal therapy upon enrolment and during the course of the study. Physiotherapy was also performed in the majority of patients during the study.

As the primary endpoint of Study 108 Part B, data on safety and tolerability (e.g. adverse events) were collected. In addition, sweat chloride measurements were performed, and lung function was measured via spirometry. The body mass index and pulmonary exacerbations as well as various laboratory parameters were also recorded. Data on health-related quality of life were not collected in Study 108. The patients included at the start of study had only the mutations G551D (n = 32) and S549R (n = 2).

Following Study 108, patients could switch to Study 109 and either continue taking ivacaftor for 84 weeks or continue without treatment. In Study 109, 33 of the 34 children switched to the ivacaftor arm. The endpoints surveyed essentially corresponded to those of Study 108.

In Studies 108 and 109 on 2- to 5-year-old children, no deaths occurred under treatment with ivacaftor.

Pulmonary exacerbations, above all those that lead to admission to hospital, represent a clinically relevant endpoint and are considered patient-relevant. In Studies 108 and 109, two different definitions for pulmonary exacerbations were used. Even when both definitions are taken into account, the frequency of pulmonary exacerbations and related hospital admissions in this age group is low.

The endpoint i.v. antibiotics therapy caused by pulmonary exacerbations does not allow any further statements (for example: on severe exacerbations) since the i.v. administration is also dependent on the pathogen spectrum and not solely correlated to the degree of severity of the pulmonary exacerbation.

The forced expiratory volume per second (FEV_1), which is represented as a percentage of the forced expiratory volume per second of standardised normal value as FEV_1 %, was measured as an absolute change over a 24-week treatment period.

In Studies 108 and 109, the endpoint forced one-second volume (FEV_1 %) was collected for too few patients to be able to provide interpretable results. The measurement in children up to 5 years old is also difficult to implement and therefore subject to uncertainties[5].

Different opinions on patient relevance to FEV_1% exist. The overall statement on the extent of the additional benefit remains unaffected.

In Studies 108 and 109, both the BMI and the BMI z-score were used as endpoints. The BMI is used to assess body weight in relation to height. In the present indication, body weight or BMI is important because developmental disorders and disturbed nutrient uptake are among the typical signs of cystic fibrosis. This endpoint is considered to be a patient-relevant morbidity parameter, especially in children with characteristic, disease-related growth disorders. Data adjusted for age and gender (z-scores) are preferred over absolute values.

At the end of the study, both studies (108 and 109) showed an improvement in the BMI z-score of ivacaftor compared with baseline. 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.

The measurement of chloride values in sweat is used as a standard diagnostic procedure because the values reflect the functionality of the CFTR protein, which is the pathophysiological cause of the disease. Because the extent of a reduction in sweat chloride concentration is not directly associated with the extent of the change in symptomatology, the endpoint is not considered to be directly relevant to patients and is considered complementary. In Study 108, there was a significant reduction in sweat chloride values after 24 weeks compared with baseline. After a further 84 weeks (Study 109) the values hardly differed from those at week 24 in Study 108.

Endpoints of the endpoint category health-related quality of life were not investigated in Studies 108 and 109.

Adverse events occurred in 33 patients each in both studies (97.1% in 108; 100% in 109). Serious adverse events occurred in six patients (17.6%) in Study 108 and 11 (33%) in Study 109. In total, one patient (2.9% in 108; 3% in 109) discontinued treatment with ivacaftor because of adverse events in both studies.

Although the studies (108 and 109) are not suitable for assessing the additional benefit compared with the appropriate comparator therapy because of their single-arm design, they provide supporting data for a transfer of the additional benefit.

[5] CHMP guideline on the clinical development of medicinal products for the treatment of cystic fibrosis (EMEA/CHMP/EWP/9147/2008).

According to the assessment report of the European Medicines Agency (EMA) from 2015, the uncontrolled Study 108 of children aged 2–5 years was accepted based on an extrapolation of efficacy data from older children and adults with the G551D mutation and various other gating mutations. The safety profile was found to be comparable to studies of older populations.

The findings of the EMA on the medical rationale for the transfer of data from older patient groups to 2 to 5-year-olds with various gating mutations are also decisive for the G-BA for an evidence transfer.

Cystic fibrosis is a hereditary multisystemic disease in which mutations in the CFTR gene cause disorders in the chloride channel of exocrine glands. The pathophysiological background (disturbance in the chloride channel) is thus identical for the patient population of 2 to 5-year-olds and the older patients. Treatment with ivacaftor modulates the functionality of the chloride channels regardless of the age of the patient.

Cystic fibrosis is progressive (i.e. its manifestation increases with age). Thus, younger patients with cystic fibrosis still have relatively few symptoms.

The lower burden of symptoms and improvement of symptoms in the ivacaftor arm is also evident in patients aged 6 to 11 years compared with patients aged 12 to 18 years (Studies 103 and 102) and support this fact (for further details, please refer to the procedure for patients aged 6 years and older with a G551D mutation).

The appropriate comparator therapy defined by the G-BA for children from 2 to 5 years of age as well as for children from 6 years of age as well as for patients from 12 years of age is identical in the presence of a gating mutation in the CFTR gene (best supportive care); this is a decisive criterion for an evidence transfer 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.

Considering the fact that there is an identical underlying genetic cause of the disease and thus a comparable pathophysiology as well as on the basis of the study data of the study for 2 to 5-year-old children (Study 108 and 109), which, compared with the results of the study of 6 to 11-year-old children with G551D mutation (Study 103) and the study of patients ≥ 12 years with G551D mutation (Study 102), shows largely similar efficacy and in view of the identical appropriate comparator therapies for the three populations a transferability of the additional benefit of the endpoint “BMI z-score” identified from the population 12- to 18-year-old and 6- to 11-year-old children with a G551D mutation to the population of 2- to 5-year-old children with the same mutation is assumed.

The G551D mutation represents the most frequent gating mutation in the CFTR gene. The presence of this mutation was the inclusion criterion for Studies 102 (12–18 years) and 103 (6–11 years) through which an additional benefit compared with the appropriate comparator therapy was shown.

The effects of ivacaftor treatment in patients aged 6 years and older with various non-G551D gating mutations[6] were investigated in an eight-week randomised, placebo-controlled cross-over study (111). Compared with BSC, advantages were shown in the FEV_1% and the BMI-z-Score as well as in the domains vitality and subjective perception of health of the CFQ-R questionnaire in patients aged 14 years and older.

Because the eight-week study duration is too short to assess the sustainability of patient-relevant endpoints, the findings of the regulatory authority EMA are taken into account. These assume a sufficient agreement of the data between week 8 in Study 111 and week 24 in Studies 102 and 103.

With regard to the positive effects observed in patients with a G551D mutation (Study 102 and 103) and assuming that comparable effects are achieved in both populations (patients with

[6] G178R, S549N, S549R, G551S, G970R (not approved), G1244E, S1251N, S1255P, G1349D.

various non-G551D mutations and patients with a G551D mutation) with ivacaftor treatment, the additional benefit of ivacaftor observed in the treatment of patients from the age of 12 years with a G551D mutation is additionally considered in the assessment of patients with various non-G551D gating mutations. Thus, an additional benefit of ivacaftor compared with BSC can be derived for patients aged 6 years and older with various non-G551D gating mutations (for further details, please refer to the benefit assessment procedure for this patient population).

The transfer of this additional benefit to younger patients – in the present benefit assessment the 2 to 5-year-old children – with cystic fibrosis and identical gating mutations is appropriate based on the argumentation presented above.

Summary

In the overall view, the G-BA concludes that the transferability of the additional benefit of ivacaftor from children and adolescents aged 6 to 11 years or 12 to 18 years to children aged 2 to 5 years with cystic fibrosis with the following gating mutations is assumed in this age group: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R, particularly against the background of the comparable clinical picture, the progressive course of the disease, and the limitations associated with conducting clinical studies in this age group. However, the additional benefit is non-quantifiable because the scientific data basis does not allow it at this stage.

Reliability of data (probability of additional benefit)

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

2.1.4 Summary of the assessment

The present assessment concerns the renewed benefit assessment (because the € 50 million turnover limit was exceeded) of the active ingredient ivacaftor (Orphan Drug).

Ivacaftor under the name Kalydeco® is approved for the treatment of children aged 12 months and older and a body weight between 7 and 25 kg with cystic fibrosis (CF) 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 present resolution relates exclusively to children aged 2 to 5 years with cystic fibrosis and the aforementioned gating mutations.

Best supportive care was determined as an appropriate comparator therapy by the G-BA.

For the benefit assessment, the pharmaceutical company presents the open, randomised, Phase III study (VX11-770-108) and its expansion study (VX11-770-109). Although the studies are not suitable for assessing the additional benefit compared with the appropriate comparator therapy because of their single-arm design, they provide supporting data for a transfer of the additional benefit.

Because of the lack of comparative data, the results for ivacaftor treatment were taken from studies with older patients (Study VX12-770-111: from 6 years of age with non-G551D gating mutations; Study VX08-770-103: 6–11 years with G551D mutation, VX08-770-102. ≥ 12 years with G551D mutation). Based on these studies, an additional benefit compared with BSC was derived for the corresponding patient groups.

Particularly against the background of the comparable clinical picture, the progressive course of the disease, and the limitations in conducting clinical studies, the G-BA concludes that the transferability of the additional benefit of ivacaftor from children and adolescents aged 6 to 11 years or 12 to 18 years to children aged 2 to 5 years with cystic fibrosis with the following gating mutations is assumed in this age group: G551D, G1244E, G1349D, G178R, G551S,

S1251N, S1255P, S549N, or S549R Because of the uncertainty caused by the transfer of the additional benefit to a younger population, a hint for a non-quantifiable additional benefit can be identified.

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

The G-BA uses the following derivation of patient numbers in order to enable a consistent examination of patient numbers, taking into account the most recent resolution (15 August 2019) 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 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[7].

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 without process data and up-to-date consent forms were not taken into account. Furthermore, there is currently no indication that the number of patients in the overall collective has changed significantly since the 2012 report (8042 patients ever reported and still alive at that time). This number has already been adjusted to eliminate multiple responses in accordance with the information in the documentation).

The number of 15–16 patients in the SHI target population calculated by the pharmaceutical company nevertheless seems plausible. For this purpose, the G-BA takes into account the patient numbers of the resolution according to Section 35a SGB V of 2 June 2016 in the same therapeutic indication (15 patients).

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: 5 February 2020):
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 February 2020).

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 potency was first determined on the basis of

[7] https://www.muko.info/ (https://www.muko.info/englisch-version/) Website of Mukoviszidose e.V. (German Cystic Fibrosis Association) [accessed 27 June 2019]

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.

The average body measurements from the official representative statistics “Microcensus 2017 - body measurements of the population” were used to calculate the dosages as a function of the body weight (average body weight of 14.1 kg for two-year-old and 20.8 kg for five-year-old children).[8]

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) 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 varies from patient to patient 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 indicated in the product information.

The patients in this therapeutic indication 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:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Ivacaftor	continuously, 2 × daily	365	1	365
Best supportive care	different for each individual patient			
Appropriate comparator therapy				
Best supportive care	different for each individual patient			

[8] German Federal Office For Statistics, Wiesbaden 2018: http://www.gbe-bund.de/

Usage and 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					
Ivacaftor	75 mg	150 mg	2 × 75 mg	365	730 × 75 mg
Best supportive care	different for each individual patient				
Appropriate comparator therapy					
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					
Ivacaftor 75 mg	56 GRA	€ 16,432.12	€ 1.77	€ 937.86	€ 15,492.49
Best supportive care	different for each individual patient				
Appropriate comparator therapy					
Best supportive care	different for each individual patient				
Abbreviations: GRA = granulate in the sachet					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 February 2020

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

Because there are no regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed and the appropriate comparator therapy according to the product information, no costs for additionally required SHI services had to be taken into account.

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 12 June 2019.

On 28 August 2019, 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 6 VerfO.

By letter dated 28 June 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 ivacaftor.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 November 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 2 December 2019. The deadline for submitting written statements was 23 December 2019.

The oral hearing was held on 7 January 2020.

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 February 2020, and the proposed resolution was approved.

At its session on 20 February 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	12 June 2019	Determination of the appropriate comparator therapy
Subcommittee Medicinal Products	7 January 2020	Conduct of the oral hearing

Working group Section 35a	14 January 2020 4 February 2020	Consultation on the dossier evaluation by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal Products	11 February 2020	Concluding discussion of the draft resolution
Plenum	20 February 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 20 February 2020

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

Prof. Hecken