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 6 Years of Age with G551D Mutation)

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 15 August 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.

At its session on 7 February 2013, the G-BA passed a resolution on the benefit assessment of ivacaftor 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, 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 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)

"Kalydeco tablets are indicated for the treatment of adults, adolescents, and children aged 6 years and older and weighing 25 kg or more 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 (see Sections 4.4 and 5.1)."

The present resolution relates exclusively to the therapeutic indication for the treatment of cystic fibrosis in patients aged 6 years and over with a body weight of at least 25 kgbearing the gating mutation G551D in the CFTR gene is present.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Patients aged 6 to 11 years with cystic fibrosis with a G551D mutation in the *CFTR* gene

Appropriate comparator therapy:

- Best supportive care.

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

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

a) Patients aged 12 years and older with cystic fibrosis with a G551D mutation in the *CFTR* gene

Appropriate comparator therapy:

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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 (Cayston®), carbocisteine[2], ceftazidim, ciprofloxacin, colistimethate, dornase alfa (Pulmozyme®), levofloxacin[3], meronem, mannitol (Bronchitol®), pancreatin, tobramycin.

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 group of patients to be considered in the present therapeutic indication, “Patients from 6 years of age with cystic fibrosis with a G551D mutation in the CFTR gene”, the G-BA has passed the following resolution:

- Resolution on ivacaftor of 7 February 2013 (*Orphan Drug* Status; is repealed with the present resolution).

[2] Approved for adolescents from 13 years and adults with CF
[3] Approved only for adult patients with CF

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. According to the current state of medical knowledge, there is no specific standard therapy for patients from the age of 6 years with cystic fibrosis who have a G551D mutation in the CFTR gene. The aforementioned medicinal and non-medicinal therapy options are available for symptomatic therapy. In the evidence provided, these are recommended for symptomatic therapy of cystic fibrosis, 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). Cystic fibrosis is thus treated individually for each patient to alleviate symptoms and improve the quality of life in the sense of best supportive care (BSC).

The 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:

a) Patients aged 6 to 11 years with cystic fibrosis with a G551D mutation in the *CFTR* gene

Hint for a non-quantifiable additional benefit

Justification:

For the assessment of the additional benefit of ivacaftor in children aged 6–11 years with cystic fibrosis who have the gating mutation G551D in the *CFTR* gene after the € 50 million turnover limit is exceeded, the Study VX08-770-103 (hereinafter Study 103) will be used. Study 103 is the pivotal, multi-centre, randomised, double-blind, placebo-controlled Phase III study, which has already been submitted for the initial evaluation of ivacaftor according to Section 35a SGB V.

Study 103 investigated the efficacy and tolerability of treatment with 150 mg ivacaftor twice daily compared with placebo, in addition to the basic therapy for the treatment of cystic fibrosis.

A total of 52 children aged between 6 and 11 years with the gating mutation G551D in at least one allele of the *CFTR* gene were included and randomly assigned at a ratio of 1:1 to the two study arms in Part B of the study, ivacaftor versus placebo. The non-randomised Part A on the pharmacokinetic investigation of a single dose of ivacaftor is not relevant for the benefit assessment.

In accordance with the inclusion criteria of Study 103, the children had to weigh at least 15 kg. This does not correspond to the minimum body weight of 25 kg for the use of ivacaftor film-coated tablets according to the product information. Therefore, only those study participants who have a minimum body weight of 25 kg and were treated with ivacaftor in accordance with the marketing authorisation will be used for the benefit assessment. This corresponds to a sub-population of 73% of the children included in Study 103: 20 children in the ivacaftor arm and 18 children in the control group.

As further inclusion criteria, the forced expiratory volume in one second (FEV_1) had to be between 40% and 105% of the standardised normal value for age, sex, and height and the diagnosis of cystic fibrosis had to be proven either by a sweat chloride value ≥ 60 mmol/l or the presence of two mutations causing cystic fibrosis. The patients were stratified according to FEV_1 at the time of screening (< 70%, 70–90%, > 90%).

With the exception of the inhalation of hyperosmolar NaCl solution, the intake of concomitant medication was permitted throughout the entire study, but differed between the study arms. A possible bias because of the imbalance cannot be excluded.

The standard inhalation of hyperosmolar NaCl solution used in Germany for patients with cystic fibrosis was not possible in the study. Based on the evidence available, it appears unclear whether therapy with hyperosmolar NaCl inhalation would have influenced the results for the patient-relevant endpoints.

From the data submitted in the dossier as well as from the data subsequently submitted in the written statement procedure, it is clear that, despite the absence of hyperosmolar NaCl inhalation therapy, the children received comprehensive symptomatic medicinal therapy, including dornase alfa, pancreatic enzymes, bronchodilators, painkillers, corsticosteroids, and vitamin preparations upon enrolment and during the course of the study. Regarding concomitant therapy with antibiotics, more than 95% of the patients started at least one new antibiotic during the course of the study. In addition, most patients who were not treated with antibiotics prior to the first administration of the study medication were also treated with antibiotics during the study. Overall, it can be assumed that at least the performed (stable) basic therapy with mucolytics and pancreas enzymes as well as antibiotics was appropriate.

The primary endpoint of the study was the absolute change in FEV_1 (as % of standardised normal value) after 24 weeks. In addition, endpoints in the categories mortality, morbidity, quality of life, and side effects were surveyed.

The treatment period was extended from 24 weeks to 48 weeks by amendment to the study protocol. For the present assessment, the results of week 48 are taken into account.

Extent and probability of the additional benefit

Mortality

No deaths occurred in Study 103.

Morbidity

Pulmonary exacerbations and hospitalisation caused by pulmonary exacerbations

Pulmonary exacerbations, above all those that lead to admission to hospital, represent a clinically relevant endpoint and are considered patient-relevant.

For the endpoints pulmonary exacerbations and hospitalisation due to pulmonary exacerbations, each operationalised on the basis of event rates (number of events per patient year), no data on effect estimation are available. For the further evaluations of patients with at least one event, there is no statistically significant difference between the treatment groups for either endpoint.

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.

Forced expiratory volume per second (FEV_1 %)

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 and relative change over a 48-week treatment period. For both absolute and relative change in the FEV_1 value over 48 weeks, there is a statistically significant difference in favour of ivacaftor + BSC compared with placebo + BSC.

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

Symptomatology measured through the Cystic Fibrosis Questionnaire-Revised (CFQ-R)

The endpoint symptomatology was assessed using the disease-specific CFQ-R (patient version; supplementary parent/carer version) and included the domains respiratory system, gastrointestinal symptoms, and weight problems *(the domain weight problems is not intended for children from 6 to 11 years and is only available in the parent/caretaker version).* The CFQ-R is a questionnaire that measures the subjective perception from the patient's perspective ("patient-reported outcome, PRO") or his or her evaluation through the parents or caretaker.

In the domain respiratory system and gastrointestinal symptoms, there is no statistically significant difference between the treatment groups for the patient version as well as for the parent/caretaker version.

In the domain weight problems in the parent/caretaker version, there was a statistically significant advantage of IVA + BSC compared with placebo + BSC. The 95% confidence interval of the Hedges' g in this case does not lie fully outside of the irrelevance range. The clinical relevance of this effect can therefore not be assessed.

Body Mass Index (BMI) and BMI z-score

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.

Study 103 shows a statistically significant difference in the BMI z-score between ivacaftor + BSC compared with placebo + BSC. However, the extent of this cannot be conclusively assessed.

Sweat chloride concentration (mmol/l)

The determination of the chloride concentration in sweat is used as a standard diagnostic procedure because the values reflect the functionality of the CFTR protein, whereby the disease is pathophysiologically determined. 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 103, the endpoint sweat chloride concentration was surveyed as an absolute change at week 48. The absolute change in sweat chloride concentration for the total population *(including children with a body weight < 25 kg)* shows a statistically significant difference in favour of ivacaftor + BSC compared with placebo + BSC.

<u>Quality of life</u>

Health-related quality of life measured through CFQ-R

The quality of life was recorded based on the validated, disease-specific quality of life instruments CFQ-R by applying the patient version (supplementary parent/caretaker version).

In the domains on health-related quality of life of the CFQ-R, neither the patient version nor the parent/caretaker version show statistically significant differences between treatment groups.

Side effects

The data on SAE are not usable because there is no information on the type of events included for the relevant sub-population *(children weighing 25 kg or more)*. The SAE of the total population also include events that can be assigned to both side effects and morbidity and therefore cannot be assessed.

For the results on the overall rate of the AE, there are no data on effect estimation.

For the endpoint discontinuation because of AE, there was no statistically significant difference between the treatment groups.

In the category side effects, there was no statistically significant difference between the treatment arms of the study in the overall view.

Overall assessment

The pivotal, multi-centre, randomised, double-blind, placebo-controlled Phase III Study 103 was submitted for the renewed benefit assessment (after exceeding the € 50 million turnover limit) of ivacaftor for the treatment of cystic fibrosis in patients aged 6 to 11 years who have the G551D mutation in the *CFTR* gene. This study provides results on mortality, morbidity, quality of life, and side effects.

No deaths occurred in Study 103.

For the endpoints pulmonary exacerbations and hospitalisation because of pulmonary exacerbations as well as in the domains of symptomatology recorded using CFQ-R in the patient version, there are no statistically significant differences between the treatment groups. In the domain weight problems in the parent/caretaker version, there is a statistically significant difference in favour of ivacaftor. However, the clinical relevance of the effect cannot be assessed.

In the endpoint BMI z-score, there is a statistically significant difference to the advantage of ivacaftor compared with the comparator arm; however, the extent of this cannot be conclusively assessed. In the present indication, the BMI or BMI z-score 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.

In the additionally shown endpoints FEV_1 and chloride concentration in sweat, there are statistically significant differences in favour of ivacaftor compared with the comparator arm.

In the health-related quality of life category, there are no statistically significant differences between treatment groups in the corresponding domains of the CFQ-R, both in the patient and parent/caretaker versions.

In the category side effects, there was no statistically significant difference between the treatment arms of the study in the overall view.

Cystic fibrosis is progressive (i.e. its manifestation increases with age). Thus, younger patients with cystic fibrosis – like the children to be considered here – still have relatively few symptoms. This means that the influence of the disease progression on patient-relevant endpoints can be measured only to a limited extent. Thus, the burden of symptoms and improvement of symptoms in the ivacaftor arm is more evident in patients aged 12 years and older than in children aged 6 to 11 years.

For older children and adolescents from 12 years of age in the present therapeutic indication, advantages for ivacaftor were found compared with the comparator arm. These include the patient-relevant endpoints BMI or BMI z-score, pulmonary exacerbations and respiratory system using CFQ-R in the morbidity category as well as other endpoints in the quality of life category using CFQ-R.

In view of the advantage in BMI or BMI z-score in both populations as well as the advantages of ivacaftor in the older patients aged 12 years and older in the above patient-relevant endpoints, considering that there is an identical underlying genetic cause of the disease and a comparable pathophysiology, the severity of the symptoms only increases with age, and taking into account the matching appropriate comparator therapies in both populations, the additional benefit established in the population of ≥ 12 year old patients is included in the overall assessment. However, because of the associated uncertainties and the limitations of the evidence available, the extent is non-quantifiable.

Based on the results of Study 103 and taking into account the results of Study 102 in patients aged 12 years and older, for ivacaftor for the treatment of cystic fibrosis in children between 6 and 11 years with a G551D mutation in the *CFTR* gene, there is an additional benefit compared with the appropriate comparator therapy. However, this is non-quantifiable because of the limited evidence of its extent. *(for a detailed description of Study 102, see below the justification for b) patients aged 12 years and older with cystic fibrosis with a G551D mutation in the CFTR gene)*

Reliability of data (probability of additional benefit)

The present assessment is based on the results of Study 103 in children aged between 6 and 11 years, taking into account the assessment of ivacaftor in patients aged 12 years and older based on Study 102. At maximum the probability of additional benefict from the Study 102 can be concluded as a hint.

In Study 103, the standard inhalation of hyperosmolar NaCl solution used in Germany for patients with cystic fibrosis was not possible. Overall, there are therefore uncertainties regarding the significance of the data because it cannot be estimated to what extent a therapy with hyperosmolar NaCl inhalation would have influenced the results for the patient-relevant endpoints.

Because of the limitations of the evidence available as well as the uncertainties of patient-relevant effects in this age group, overall is a hint derived.

b) Patients aged 12 years and older with cystic fibrosis with a G551D mutation in the *CFTR* gene

Hint for a considerable additional benefit

Justification:

For the assessment of the additional benefit of ivacaftor in patients aged 12 years and older with cystic fibrosis who have the gating mutation G551D in the *CFTR* gene after the € 50 million turnover limit is exceeded, the Study VX08-770-102 (hereinafter Study 102) will be used. Study 102 is the pivotal, multi-centre, randomised, double-blind, placebo-controlled Phase III study, which has already been submitted for the initial evaluation of ivacaftor according to Section 35a SGB V.

Study 102 investigated the efficacy and tolerability of treatment with 150 mg ivacaftor twice daily compared with placebo, in addition to the basic therapy for the treatment of cystic fibrosis.

A total of 167 patients aged 12 years and older with the gating mutation G551D in at least one allele of the *CFTR*-gene were included and randomly assigned at a ratio of 1:1 to the two study arms, ivacaftor versus placebo. The body weight for all patients included in the study was at least 25 kg. Thus, for the entire study population, ivacaftor was used in compliance with the marketing authorisation.

As an inclusion criterion, among other things, the forced expiratory volume in one second (FEV_1) had to be between 40% and 105% of the standardised normal value for age, sex, and

height and the diagnosis of cystic fibrosis had to be proven either by a sweat chloride value ≥ 60 mmol/l or the presence of two mutations causing cystic fibrosis. The patients were stratified according to age (< 18 years vs ≥ 18 years) and FEV_1 at the time of screening (< 70% vs ≥ 70%).

With the exception of the inhalation of hyperosmolar NaCl solution, the intake of concomitant medication was permitted throughout the entire study but differed between the study arms. A possible bias because of the imbalance cannot be excluded.

The standard inhalation of hyperosmolar NaCl solution used in Germany for patients with cystic fibrosis was not possible in the study. Based on the evidence available, it appears unclear whether therapy with hyperosmolar NaCl inhalation would have influenced the results for the patient-relevant endpoints.

From the data submitted in the dossier as well as from the data subsequently submitted in the written statement procedure, it is clear that, despite the absence of hyperosmolar NaCl inhalation therapy, the children received comprehensive symptomatic medicinal therapy, including dornase alfa, pancreatic enzymes, bronchodilators, painkillers, corsticosteroids, and vitamin preparations upon enrolment and during the course of the study. Regarding concomitant therapy with antibiotics, more than 95% of the patients started at least one new antibiotic during the course of the study. In addition, most patients who were not treated with antibiotics prior to the first administration of the study medication were also treated with antibiotics during the study. Overall, it is to be assumed that at least the performed(stable) basic therapy with mucolytics and pancreas enzymes as well as antibiotics was appropriate.

The primary endpoint of the study was the absolute change in FEV_1 (as % of standardised normal value) after 24 weeks. In addition, endpoints in the categories mortality, morbidity, quality of life, and side effects were surveyed.

The treatment period was extended from 24 weeks to 48 weeks by amendment to the study protocol. For the present assessment, the results of week 48 are taken into account.

Extent and probability of the additional benefit

Mortality

No deaths occurred in Study 102.

Morbidity

Pulmonary exacerbations and hospitalisation caused by pulmonary exacerbations

Pulmonary exacerbations, above all those that lead to admission to hospital, represent a clinically relevant endpoint and are considered patient-relevant.

For the endpoint pulmonary exacerbations, operationalised on the basis of event rates (number of events per patient year), there was a statistically significant advantage of ivacaftor + BSC compared with placebo + BSC.

For the endpoint hospitalisation because of pulmonary exacerbations, there are no statistically significant differences between the treatment groups.

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.

Forced expiratory volume per second (FEV_1 %)

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 and relative change over a 48-week treatment period. For both absolute and relative change in the FEV_1 value over 48 weeks, there is a statistically significant difference in favour of ivacaftor + BSC compared with placebo + BSC.

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

Symptomatology measured through the Cystic Fibrosis Questionnaire-Revised (CFQ-R)

The endpoint symptomatology was assessed using the disease-specific CFQ-R (patient version) and included the domains respiratory system, gastrointestinal symptoms, and weight problems. The CFQ-R is a questionnaire that measures the subjective perception from the patient's perspective ("patient-reported outcome, PRO") or his or her evaluation through the parents or caretaker.

In the domain respiratory system, there is a statistically significant difference in favour of ivacaftor + BSC compared with placebo + BSC. The 95% confidence interval of the Hedges' g is completely outside the irrelevance threshold. This is interpreted as a clinically relevant effect.

In the domains of gastrointestinal symptoms and weight problems, there are no statistically significant differences between the treatment groups.

Health status (EQ-5D VAS)

The health status was surveyed using the VAS of the EQ-5D. Here the patient estimates the current health status on a VAS of 0 mm to 100 mm. 0 mm stands for the worst health status imaginable and 100 mm for the best.

The assessment of the health status by means of a VAS is classified as patient-relevant. Study 102 showed no statistically significant differences between the treatment groups.

Body Mass Index (BMI) and BMI z-score

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.

Study 102 showed a statistically significant difference in the BMI z-score between ivacaftor + BSC compared with placebo + BSC. However, the extent of this cannot be conclusively assessed.

Sweat chloride concentration (mmol/l)

The determination of the chloride concentration in sweat is used as a standard diagnostic procedure because the values reflect the functionality of the CFTR protein, whereby the disease is pathophysiologically determined. 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 102, the endpoint sweat chloride concentration was surveyed as an absolute change at week 48. For the absolute change in sweat chloride concentration, there is a statistically significant difference in favour of ivacaftor + BSC compared with placebo + BSC.

Quality of life

Health-related quality of life measured through CFQ-R

The quality of life was recorded based on the validated, disease-specific quality of life instruments CFQ-R by applying the patient version.

In the domains of physical well-being, vitality, and subjective perception of health, there are statistically significant differences in favour of ivacaftor + BSC compared with placebo + BSC.
In the domain of subjective perception of health in patients aged 14 years and older, the 95% confidence interval of the Hedges' g is completely outside the irrelevance range. The effect is therefore interpreted as clinically relevant.
For the domains physical well-being and vitality (vitality in patients 14 years of age and older), there is an effect modification by feature FEV_1 at the start of study. In patients with an $FEV_1 < 70\%$ at the start of study, the 95% confidence interval of the Hedges' g is completely outside the irrelevance range. Thus, a clinically relevant effect can only be assumed for these patients. For patients with an $FEV_1 \geq 70\%$, there were no statistically significant differences between the treatment groups in the domains of well-being and vitality.

For the remaining domains, either there is no statistically significant difference between the treatment groups or, if statistical significance is present, the clinical relevance of the effect cannot be assessed because the 95% confidence interval of the Hedges' g is partly within the irrelevance range.

Side effects

The data on SAE are not usable because, among other things, events that can be attributed to both side effects and morbidity have been recorded and can therefore not be assessed.

For the results on the overall rate of the AE, there are no data on effect estimation.

For the endpoint discontinuation because of AE, there was no statistically significant difference between the treatment groups.

For the specific AE rash and dizziness, there is a statistically significant difference to the disadvantage of ivacaftor + BSC compared with placebo + BSC.

Overall assessment

The pivotal, multi-centre, randomised, double-blind, placebo-controlled Phase III Study 102 was submitted for the renewed benefit assessment (after exceeding the € 50 million limit) of ivacaftor for the treatment of cystic fibrosis in patients aged 12 years and older who have the G551D mutation in the *CFTR* gene. This study provides results on mortality, morbidity, quality of life, and side effects.

No deaths occurred in Study 102.

For the endpoints pulmonary exacerbations and symptomatology in the respiratory domain measured by CFQ-R, there are statistically significant and clinically relevant advantages in favour of ivacaftor compared with the comparator arm.

In the endpoint BMI z-score, there is a statistically significant difference to the advantage of ivacaftor compared with the comparator arm; however, the extent of this cannot be conclusively assessed.

Also in the additionally shown endpoints FEV_1 and change of the sweat chloride concentration, there are statistically significant differences in favour of ivacaftor compared with the comparator arm.

In the category health-related quality of life, the domains of the CFQ-R corresponding to the quality of life were assessed. For the domain of subjective perception of health in patients aged 14 years and older, a statistically significant and clinically relevant difference in favour

of ivacaftor compared with placebo was found. In the domains of physical well-being and vitality *(the latter only for patients aged 14 years and older)*, there is also a statistically significant and clinically relevant difference in favour of ivacaftor compared with placebo.

In the side effects category, there are statistically significant differences in favour of ivacaftor compared with placebo for the specific AE dizziness and rash; these are not more than negligible in extent.

In the overall view of the results, a considerable additional benefit of ivacaftor compared with the appropriate comparator therapy can be derived for patients from 12 years of age in the present therapeutic indication.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of Study 102 in patients aged 12 years and older. The risk of bias at the study level is classified as low.

The risk of bias at the endpoint level is rated as high overall. Differences between the treatment arms in the proportions of randomised patients included in the evaluation can be determined in the endpoints on symptomatology of the morbidity category and in the category health-related quality of life using CFQ-R. Furthermore, no statements can be made about SAE because the data is not usable.

Furthermore, in the study, the standard inhalation of hyperosmolar NaCl solution used in Germany for patients with cystic fibrosis was not possible. Overall, there are therefore uncertainties regarding the significance of the data because it cannot be estimated to what extent a therapy with hyperosmolar NaCl inhalation would have influenced the results for the patient-relevant endpoints.

Against the background of the limitations mentioned above and because only one study is available, the G-BA comes to the conclusion that at maximum a hint can be derived as a reliability of data.

2.1.4 Summary of the assessment

The present assessments is a renewed benefit assessment of the new medicinal product Kalydeco® with the active ingredient ivacaftor after the € 50 million turnover limit was exceeded. Ivacaftor is used to treat cystic fibrosis in patients 6 years of age and older who have one of the following gating mutations (class III) in the *CFTR* gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R. Based on the data presented, only statements on the G551D mutation can be made.

Ivacaftor has received marketing authorisation as an orphan drug.

In the therapeutic indication to be considered, two patient groups were distinguished.

a) Patients aged 6 to 11 years with cystic fibrosis with a G551D mutation in the *CFTR* gene.

and

b) Patients aged 12 years and older with cystic fibrosis with a G551D mutation in the *CFTR* gene.

About patient group a)

Best supportive care was determined as an appropriate comparator therapy by the GBA.

To demonstrate the additional benefit of ivacaftor, the pharmaceutical company presents the results of the randomised, double-blind, placebo-controlled Study 103 in which the administration of ivacaftor or placebo, in each case in addition to the basic therapy for the

treatment of cystic fibrosis, is investigated in children aged 6 to 11 years with the G551D mutation in the *CFTR* gene.

On the basis of Study 103, there is a statistically significant effect in favour of ivacaftor compared with the comparator arm in the endpoint BMI z-score. However, the extent of this cannot be conclusively assessed. Because the children included still show relatively few symptoms because of their young age, the results of Study 102 in patients aged 12 years and older are also taken into account in the present case. For older children and adolescents from 12 years of age in the present therapeutic indication, advantages for ivacaftor were found compared with the comparator arm. These include the patient-relevant endpoints of the morbidity category pulmonary, exacerbations and respiratory system using CFQ-R as well as BMI or BMI z-score. However, the extent of this cannot be conclusively assessed. Other endpoints in the quality of life category using CFQ-R also show advantages for ivacaftor compared with best supportive care.

Based on the results of Study 103 and taking into account the results of Study 102 in patients aged 12 years and older, for ivacaftor for the treatment of cystic fibrosis in children between 6 and 11 years with a G551D mutation in the *CFTR* gene, there is an additional benefit compared with the appropriate comparator therapy. However, this is non-quantifiable because of the limited evidence of its extent. With respect to the reliability of data (probability of additional benefit), in total a hint can be assumed.

About patient group b)

Best supportive care was determined as an appropriate comparator therapy by the GBA.

To demonstrate the additional benefit of ivacaftor, the pharmaceutical company presents the results of the randomised, double-blind, placebo-controlled Study 102 in which the administration of ivacaftor or placebo, in each case in addition to the basic therapy for the treatment of cystic fibrosis, is investigated in patients from 12 years of age with the G551D mutation in the *CFTR* gene.

On the basis of Study 102, there were advantages for ivacaftor compared with the comparator arm in the morbidity category in the patient-relevant endpoints pulmonary exacerbations and respiratory system using CFQ-R as well as in the BMI or BMI z-score. However, the extent of this cannot be conclusively assessed. Other endpoints in the quality of life category using CFQ-R also show advantages for ivacaftor compared with the comparator arm.

In the side effects category, there are statistically significant differences in favour of ivacaftor compared with placebo for the specific AE dizziness and rash; these are not more than negligible in extent.

There were no deaths in the study.

In the overall view of the results, a hint for a considerable additional benefit of ivacaftor compared with the appropriate comparator therapy can be derived for patients from 12 years of age in the present therapeutic indication.

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

a) Patients aged 6 to 11 years with cystic fibrosis with a G551D mutation in the *CFTR* gene

and

b) Patients aged 12 years and older with cystic fibrosis with a G551D mutation in the *CFTR* gene

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[4].

This figure differs from the calculation in the dossier by the pharmaceutical company, which assumes a total population of 6106 patients with cystic fibrosis. However, this figure is subject to uncertainties and represents an underestimate because patients 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 160 patients in the SHI target population calculated by the pharmaceutical company is an underestimate. Calculations of the IQWIG using the proportional values for the respective mutations determined by the pharmaceutical company result in 210 patients in the SHI target population of patients aged 6 years and older in the present therapeutic indication. According to the information provided by the pharmaceutical company, a proportion of 14.75% of patients aged 6 to 11 years is assumed. This corresponds to approx. 30 patients in patient group a). Therefore, in patient group b), approx. 180 patients can be removed.

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.

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

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 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.

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				
Patient population a) and b)				
Ivacaftor	continuously, 2 × daily	365	1	365
Best supportive care	different for each individual patient			
Appropriate comparator therapy				
Patient population a) and b)				
Best supportive care	different for each individual patient			

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					
Patient population a) and b)					
Ivacaftor	150 mg	300 mg	2 × 150 mg	365	730 × 150 mg
Best supportive care	different for each individual patient				
Appropriate comparator therapy					
Patient population a) and b)					
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					
Patient population a) and b)					
Ivacaftor 150 mg	56 FCT	€ 16,432.12	€ 1.77	€ 937.86	€ 15,492.49
Best supportive care	different for each individual patient				
Appropriate comparator therapy					
Patient population a) and b)					
Best supportive care	different for each individual patient				
Abbreviations: FCT = film-coated tablets					

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.

By letter dated 7 January 2020, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 31 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, Commissioning of the IQWiG with the supplementary assessment of documents
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