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, Various Gating Mutations)

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.

On 28 July 2014, ivacaftor received the marketing authorisation for a new therapeutic indication for the treatment of cystic fibrosis (CF, cystic fibrosis) in patients aged six years and older with one of the following gating mutations (class III) in the *CFTR* gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R. The therapeutic indication has thus been extended by the following gating mutations: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, and S549R. By resolution of 19 February 2015, the new therapeutic indication was assessed 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)

“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 older with a body weight of at least 25 kg bearing one of the following gating mutations in the CFTR gene is present: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R (non-G551D-mutation).

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

[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.

Patients aged at least 6 years and older with cystic fibrosis who have one of the following gating (class III) mutations in the *CFTR* gene G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R

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).

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 patient group to be considered in the present therapeutic indication *"patients aged 6 years and older with cystic fibrosis who have one of the following gating (class III) mutations in the CFTR gene: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R*, the G-BA has passed the following resolution:

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

- Resolution on ivacaftor of 19 February 2015 (*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 6 years and older with cystic fibrosis who have one of the following gating (class III) mutations in the *CFTR* gene G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R, 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 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:

Patients aged 6 years and older with cystic fibrosis who have one of the following gating (class III) mutations in the *CFTR* gene G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R

Hint for a non-quantifiable additional benefit

Justification:

For the assessment of the additional benefit of ivacaftor in patients aged 6 years and older with cystic fibrosis who have one of the following gating (class III) mutations in the CFTR gene: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R after the € 50 million turnover limit was exceeded, the pharmaceutical company presents the Study VX12-770-111 (hereinafter Study 111). The pivotal Study 111 was already available for the assessment of the additional benefit of ivacaftor after extension of the therapeutic indication for use in the presence of the aforementioned mutations.

Study 111 is a two-part study. Part 1 of the study consists of a randomised, double-blind Phase III cross-over design in which twice daily treatment with 150 mg ivacaftor or placebo, each in addition to the basic therapy for the treatment of cystic fibrosis, was studied for a period of eight weeks. In Part 2, an open treatment phase follows; this is not considered here for lack of a direct comparison.

A total of 39 patients aged 6 years and older with one of nine mutations in the *CFTR* gene *(one of which was not included in the marketing authorisation)* were included. Patients were detected having cystic fibrosis as a chronic sinopulmonary disease. In addition, the patients either had to have a sweat chloride value ≥ 60 mmol/l or carry two cystic fibrosis-causing mutations. Excluded from the study were patients with a forced expiratory volume in one second (FEV_1) of < 40% of the standardised normal value. Patients with the most frequent gating mutation, G551D, which corresponds to the therapeutic indication of the initial evaluation of ivacaftor, were also explicitly excluded from the study. In Study 111, eight children

aged 6 to 11 years (approx. 20%) and 11 children or adolescents aged 12 to 17 years (approx. 28%) were examined. About half of the patients were adults. Because of the small number of cases for the 6- to 11-year-olds, the assessment of the additional benefit is carried out jointly for all age groups.

According to the cross-over design, patients were randomised to two treatment sequences; 20 patients were assigned to treatment sequence 1 *(8 weeks ivacaftor + BSC; 4–8 weeks washout period; 8 weeks placebo + BSC)*, and 19 patients were assigned to treatment sequence 2 *(like sequence 1 but in reverse order)*. The patients were stratified according to age (6 to 11 years, 12 to 17 years, and ≥ 18 years) and FEV_1 at the time of screening (< 70%, 70 to 90%, > 90%).

With the exception of the inhalation of hyperosmolar NaCl solution, the intake of concomitant medication was permitted throughout the entire study. 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 patients received comprehensive symptomatic medicinal therapy, including dornase alfa, pancreatic enzymes, and bronchodilators as well as antibiotics, painkillers, corticosteroids, and vitamin preparations upon enrolment and during the course of the study. Overall, it can be assumed that at least anappropriate (stable) basic therapy with mucolytics and pancreas enzymes was carried out.

The primary endpoint of the study was the absolute change in FEV_1 (as % of standardised normal value) after 8 weeks. In addition, endpoints in the categories mortality, morbidity, quality of life, and side effects were surveyed.

The eight-week treatment phase chosen by the pharmaceutical company was considered sufficient for marketing authorisation to demonstrate the efficacy or the efficacy profile of ivacaftor and was used by the G-BA in the benefit assessment under orphan criteria for which an additional benefit is generally considered proven.

However for evaluating the effects on patient-relevant outcomes of a medicinal product that is now subject to an unrestricted benefit assessment, this study duration is too short in order to be able to make a valid assessment of the additional benefit for a chronic disease.

Cystic fibrosis is a chronic disease without a cure and with progressive disease progression and lifelong therapeutic obligation. The guideline of the European Medicines Agency (EMA) stipulates a minimum duration of six months for the investigation of a clinical endpoint in the present indication.

A treatment phase of only eight weeks does not take into account the patient-individual fluctuations in clinical symptomatology, which can be modified by various factors. Furthermore, no statements can be made on the basis of short-term studies as to whether the short-term effects persist in the longer term. Nor can any effects that only become apparent in the longer term (e.g. pulmonary exacerbations and their consequences or AE) be recorded. Pulmonary exacerbations are a common cause of lung damage or death in patients with cystic fibrosis.

In the therapeutic indication of cystic fibrosis, short-term studies (with a treatment duration of less than 24 weeks) are therefore unsuitable for the benefit assessment here.

Because of the rarity of the mutations to be investigated and because children are affected in the present therapeutic indication, Study 111 will be considered additionally in the assessment of the additional benefit of ivacaftor despite the limitations mentioned above.

Because the eight-week study duration is too short overall to assess patient-relevant endpoints, the findings of the EMA are also taken into account in the present case. In the context of the marketing authorisation of ivacaftor for the aforementioned mutations, Study 111 is compared with Studies VX08-770-102 (hereinafter Study 102) and VX08-770-103 (hereinafter Study 103) in patients with a G551D mutation.

The randomised, double-blind, controlled Phase III (RCT) Study 102 examines the efficacy and safety of ivacaftor compared with placebo, both in addition to standard therapy for the treatment of cystic fibrosis in patients aged 12 years and older who have the G551D mutation in the *CFTR* gene. The results after 48 months of treatment show an advantage for ivacaftor in the morbidity endpoints pulmonary exacerbations and symptomatology *(respiratory system of the CFQ-R domain)* and in quality of life endpoints *(domains subjective perception of health, physical well-being, and vitality of the CFQ-R)* as well as in the endpoints FEV_1, BMI z-score, and BMI.
The RCT Study 103 also investigates efficacy and safety endpoints in children aged 6 to 11 years with a G551D mutation after 48 months of treatment with ivacaftor or placebo, both as an adjunct to standard therapy for cystic fibrosis. In these children, who are in a less advanced stage of the disease than the older patients aged 12 years and older, an advantage for ivacaftor compared with control is shown only in the endpoints FEV_1, BMI z-Score and BMI *(for a detailed description of Studies 102 and 103, please refer to the justification on the resolution of ivacaftor – G551D mutation)*.
Against the background that a response to treatment with ivacaftor is predominantly seen in older patients in a more advanced stage of cystic fibrosis, the results of Study 102 are taken into account in support of the present assessment.

In accordance with the assessment of the EMA, the results of the endpoints examined at week 8 in Studies 102 and 103 are similar to the results of Study 111 presented here. With regard to the predictability of the efficacy and safety endpoints in Studies 102 and 103 at week 24 in relation to the data at week 8, the EMA assumed a sufficient agreement of the results between week 8 and week 24. However, in this context, the regulatory authority points out that these findings are based on *post hoc* analyses[4] and that the conclusions drawn from them should therefore be interpreted carefully.

Considering the advantages of ivacaftor in patients with a G551D mutation in Study 102 *(pulmonary exacerbations, symptomatology, and health-related quality of life)* and assuming that in both populations of the Studies 111 and 102, respectively, comparable effects with ivacaftor beyond eight weeks of treatment can be expected and given the identical appropriate comparator therapies, in the present case, the established additional benefit of ivacaftor in the treatment of patients from the age of 12 years with a G551D mutation is considered. However, because of the associated uncertainties, the extent is non-quantifiable.

In the following, the results of the eight-week Study 111 are additionally shown.

Extent and probability of the additional benefit

Mortality

No deaths occurred in Study 111.

[4] https://www.ema.europa.eu/en/documents/variation-report/kalydeco-h-c-2494-ii-0009-epar-assessment-report-variation_en.pdf [Last access: 29 January 2020]

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 are no statistically significant differences between the treatment groups.

For the endpoint hospitalisation caused by pulmonary exacerbations, no calculations on the statistical significance of the group difference are available.

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 an eight-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/caretaker version) and included the domains respiratory system, gastrointestinal symptoms, and weight problems *(the domain weight problems is only present in the patient version for patients aged 14 and over. The parent/caretaker version is available for younger patients from 6 to 13 years)*. 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 in the patient version, there is a statistically significant difference in favour of ivacaftor + BSC compared with placebo + BSC for patients 12 years and older. The 95% confidence interval of Hedges' g is completely outside the irrelevance threshold. There is thus a relevant effect.

In the gastrointestinal symptoms domain, there is no statistically significant difference between the treatment arms for patients aged 12 years and older. However, in these patients an effect modification by the characteristic of the presence of a *Pseudomonas aeruginosa* infection is detected at the start of study. For patients without *Pseudomonas aeruginosa* infection at the start of study, there is a statistically significant advantage of ivacaftor + BSC compared with placebo + BSC with a 95% confidence interval of the Hedges' g that is completely outside the irrelevance range. This is interpreted as a clinically relevant effect only in patients without *Pseudomonas aeruginosa* infection at the start of study.

In the domain of weight problems in patients 14 years of age and older as well as in the domains of symptomatology in patients between 6 and 11 years of age in the patient version and in the parent/caretaker version, there are 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.

In Study 111, for the BMI z-score and the additionally presented endpoint BMI (each as an absolute change after eight weeks compared with baseline), there was a statistically significant difference to the advantage of 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 111, the endpoint sweat chloride concentration was surveyed as an absolute change at week 8. 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 vitality and subjective perception of health, there are statistically significant differences in favour of ivacaftor + BSC compared with placebo + BSC in patients aged 14 years and older. Here the 95% confidence interval of the Hedges' g is completely outside the irrelevance range. The effect is therefore interpreted as clinically relevant.

For the other domains in the patient version, there are no statistically significant differences between the treatment groups.

In the parent/caretaker version, a statistically significant difference between the treatment arms only shows up in the domain of physical well-being. However, the 95% confidence interval of the Hedges' g is not completely outside the irrelevance range. The clinical relevance of this effect can therefore not be assessed.

Side effects

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

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

In the eight-week treatment phase, there were no discontinuations because of AE.

Summary:

All in all, ivacaftor for the treatment of cystic fibrosis in children from 6 years of age in the present therapeutic indication with various gating mutations, taking into account the results of Study 102 in patients from 12 years of age with a G551D mutation and Study 111, which is additionally shown here, there is an additional benefit compared with the appropriate comparator therapy. Because of the limited evidence available, the additional benefit is non-quantifiable.

Overall assessment

For the renewed benefit assessment of ivacaftor for the treatment of cystic fibrosis in patients aged 6 years and older who have one of the following gating mutations (class III) in the *CFTR* gene: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R after the € 50 million turnover limit is exceeded, the two-part Study 111, which was the basis for marketing authorisation, was submitted. Study 111 consists of an eight-week treatment with ivacaftor or placebo in addition to basic therapy (Part 1). The subsequent open treatment phase (Part 2) is not considered here.

Despite the fact that the study was too short to assess the patient-relevant endpoints, the study will be additionally considered because of the rarity of the mutations to be investigated and the fact that children are affected. In the overall view of the results of Study 111, the endpoint BMI z-score shows a statistically significant effect in favour of ivacaftor compared with the comparator arm; however, the extent of this cannot be conclusively assessed. In the category health-related quality of life, the endpoints vitality and subjective perception of health in patients aged 14 years and older show statistically significant and clinically relevant advantages for ivacaftor compared with the control arm. In the other recorded endpoints of the categories morbidity, quality of life, mortality, and side effects, there are no statistically significant differences between treatment groups.

Because the eight-week study duration is too short to assess patient-relevant endpoints, the findings of the EMA are taken into account in the present case to assess the long-term effects of ivacaftor. Accordingly, it can be assumed that the results of the studies evaluated here (Study 111 with Studies 102 and 103) are sufficiently comparable at week 8 in patients with a G551D mutation. In these studies, after 48 weeks of ivacaftor treatment, an advantage was shown in the endpoint FEV_1 as well as in the endpoints BMI and BMI z-score. However, the extent of this cannot be conclusively assessed. In addition, Study 102 showed an advantage for ivacaftor in the patient-relevant endpoints of morbidity and health-related quality of life in patients 12 years and older. In view of the concordant appropriate comparator therapies of both studies, the established additional benefit of ivacaftor in the treatment of patients from the age of 12 years with a G551D mutation will be considered. However, because of the associated uncertainties, the limitations of the evidence available, and the short study duration of Study 111, the extent is non-quantifiable.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of Study 111 in patients aged 6 years and older with various gating mutations, taking into account the evaluation of ivacaftor in patients aged 12 years and older with a G551D mutation based on Study 102. At maximum the probability of additional benefict from the Study 102 can be concluded as a hint.

In Study 111, 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 (Study 111 with too short a study duration of eight weeks) as well as the uncertainties that arise when comparing the effects of ivacaftor in patients in the present therapeutic indication with various gating mutations with the patient population with the G551D mutation, a hint regarding the reliability of data can be derived.

2.1.4 Summary of the assessment

The present assessment 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 aforementioned mutations – with the exception of the G551D mutation – can be made.

Ivacaftor has received marketing authorisation as an orphan drug.

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

To demonstrate the additional benefit of ivacaftor, the pharmaceutical company presents the results of Part 1 of the randomised, double-blind, placebo-controlled Study 111 in which the administration of ivacaftor or placebo, both in addition to the basic therapy for the treatment of cystic fibrosis, is investigated in patients in the present therapeutic indication for a period of eight weeks.

Because the study was too short to assess patient-relevant outcomes, the study will be considered additionally. In the overall view of the results of Study 111, the endpoint BMI z-score shows a statistically significant effect in favour of ivacaftor compared with the comparator arm; however, the extent of this cannot be conclusively assessed. In the category health-related quality of life, the endpoints vitality and subjective perception of health in patients aged 14 years and older show statistically significant and clinically relevant advantages for ivacaftor compared with the control arm. In the other recorded endpoints of the categories morbidity, quality of life, mortality, and side effects, there are no statistically relevant differences between treatment groups.

Based on the findings of the EMA on the comparability of the results of Study 111 with the results of Studies 102 and 103 at week 8 in patients with a G551D mutation, the established additional benefit of ivacaftor in the 48-month treatment of patients from the age of 12 years with a G551D mutation is taken into account.

All in all, ivacaftor for the treatment of cystic fibrosis in children from 6 years of age in the present therapeutic indication with various gating mutations results in an additional benefit compared with the appropriate comparator therapy. However, because of the limited evidence available, the extent of this is non-quantifiable. With respect to the reliability of data (probability of additional benefit), in total a hint can be assumed.

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

Patients aged 6 years and older with cystic fibrosis who have one of the following gating (class III) mutations in the *CFTR* gene G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R

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[5].

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 2 to 4 patients in the SHI target population calculated by the pharmaceutical company is an underestimate.

The G-BA takes into account the patient numbers of the resolution according to Section 35a SGB V of 19 February 2015 in the same therapeutic indication.

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

[5] 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.

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			

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	150 mg	300 mg	2 × 150 mg	365	730 × 150 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 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					
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.

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