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 (New Therapeutic Indication: Cystic Fibrosis, Patients ≥ 6 months to < 18 Years (R117H))

of 17 December 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 based on 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.

In its previously approved therapeutic indications, sales of ivacaftor within the German statutory health insurance system at pharmacy sales prices including VAT exceeded € 50 million necessitating the submission of evidence for ivacaftor according to Section 5 paragraphs 1 to 6 of the Rules of Procedure (VerfO) of the G-BA to demonstrate its additional benefit compared to the appropriate comparator therapy.

On 9 June 2020, ivacaftor received the marketing authorisation for a new therapeutic indication classified as a major type 2 variation according to Annex 2, number 2a to Regulation (EC) No. 1234/2008 of the Commission from 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

On 25 June 2020, the pharmaceutical company submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient ivacaftor with the new therapeutic indication (cystic fibrosis, patients ≥ 6 months to < 18 years with *R117H* mutation) in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

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 1 October 2020, 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 written statements made in the written 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 based on their therapeutic relevance (qualitative) according to 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 written 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

Kalydeco granules are indicated for the treatment of infants aged at least 6 months, toddlers and children weighing 5 kg to less than 25 kg with cystic fibrosis (CF) who have an *R117H CFTR* mutation or one of the following gating (class III) mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R*.

Kalydeco tablets are indicated as monotherapy 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 an *R117H CFTR* mutation or one of the following gating (class III) mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R*.

[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.

Therapeutic indication of the resolution (resolution of 17 December 2020):

Kalydeco is indicated for the treatment of patients from 6 months to < 18 years of age with cystic fibrosis (CF) who have an *R117H-CFTR* mutation.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Patients from 6 months to < 6 years of age with cystic fibrosis who have an *R117H* mutation in the *CFTR* gene:

Appropriate comparator therapy for ivacaftor as monotherapy:

- 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 Heilmittel-Richtlinie (Remedies Directive)), making full use of all possible dietary measures).

b) Patients from 6 years to < 18 years of age with cystic fibrosis who have an *R117H* mutation in the *CFTR* gene:

Appropriate comparator therapy for ivacaftor as monotherapy:

- 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 Heilmittel-Richtlinie (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 applications or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

On 1. The following medicinal products are approved for symptomatic therapy of CF: Aztreonam[2], carbocisteine[3], ceftazidim, ciprofloxacin, colistimethate, dornase alfa, levofloxacin[4], meronem, mannitol[4], pancreatin, tobramycin[2].

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

On 3. No resolutions are available for the patient group “patients from 6 months to < 18 years of age with cystic fibrosis who have *R117H* mutations in the *CFTR* gene” to be considered in the therapeutic indication.

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 months to 18 years with cystic fibrosis with an *R117H* mutation, there is no specific standard therapy according to the current state of medical knowledge. The aforementioned medicinal and non-medicinal therapy options are available for symptomatic therapy. In the evidence provided, these are recommended for symptomatic therapy of CF, in particular, antibiotic therapy of pulmonary infections (ceftazidine, colistimethate, tobramycin), inhalation of medicinal products (mannitol, dornase alfa), enzyme substitution for pancreatic insufficiency (pancreatin), and nutritional therapy and support of respiratory function (e.g. through physiotherapy). CF is thus treated 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) For patients from 6 months to < 6 years of age with cystic fibrosis who have an *R117H* mutation in the *CFTR* gene, there is a hint for a non-quantifiable additional benefit.

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

Justification:

For the benefit assessment of ivacaftor in children from 6 months to < 6 years with cystic fibrosis who have an *R117H* mutation in the *CFTR* gene, the pharmaceutical company does not submit data from studies compared with BSC. In addition, data from the observational study VX15-770-122 (hereinafter referred to as study 122) were presented in the dossier; however, these were not used by the pharmaceutical company to derive the additional benefit. Without differentiating between patient populations a) and b), the pharmaceutical company transfers the results of ivacaftor treatment in adults with the same mutation to patients 6 months and older.

Study 122 is an ongoing observational study that collected available data from the US Cystic Fibrosis Foundation registry of patients aged between 2 years to < 18 years with *R117H* mutation. In the dossier, the data for 36 months before and after the start of therapy with ivacaftor are presented additionally in a purely descriptive form. Because this does not answer any questions regarding the determination of additional benefit, the study is not used for the present benefit assessment. However, it does provide supporting data for evidence transfer.

In Study 122, among other things, the change in BMI z-score from the start of therapy to > 0 to 12 months, > 12 to 24 months, and > 24 to 36 months thereafter was assessed. The BMI is used to assess body weight in relation to height. In the present indication, body weight and height 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 sex (z-scores) are preferred over absolute values.
Although only a descriptive evaluation was carried out in the study, there seems to be no relevant change here. However, it cannot be conclusively assessed to what extent the increasing age and development of the patients influence the result.

The European Medicines Agency extrapolated data from adults to demonstrate efficacy and extrapolated data from children with gating mutations to demonstrate safety as part of the marketing authorisation of ivacaftor in children 6 months to < 18 years of age with an *R117H* mutation.

The findings of the European Medicines Agency (EMA)[5] on the medical rationale of transferring the data from older patient groups or patients with other mutations to the children from 6 months to < 6 years with *R117H* mutation are also decisive for the G-BA in deriving the additional benefit in the present benefit assessment.

Cystic fibrosis is a hereditary multisystemic disease in which mutations in the *CFTR* gene cause disorders in the chloride channel of exocrine glands. The pathophysiological background (disturbance in the chloride channel) is thus identical for the patient population of children aged 6 months to < 6 years and the older patients. Treatment with ivacaftor modulates the functionality of the chloride channels regardless of the age of the patient.

[5] Assessment report, Kalydeco, EMA/297262/2020 from 30 April 2020; available at www.ema.europa.eu/en/documents/variation-report/kalydeco-h-c-2494-ii-0082-epar-assessment-report-variation_en.pdf

Cystic fibrosis is progressive (i.e. its manifestation increases with age). Thus, younger patients with cystic fibrosis still have relatively few symptoms. Accordingly, the older patient population b (6 to < 18-year-old patients with the same mutation in the *CFTR* gene) showed only a minor burden of symptoms in Study VX11-770-110. Therefore, it cannot be assumed that the effects of treatment could be reproduced in this even younger age group.

In adult patients with cystic fibrosis and an *R117H* mutation, a hint for a minor additional benefit had been derived in the resolution of 20 February 2020. In Study 110, ivacaftor showed an advantage over the appropriate comparator therapy BSC both in the symptomatology of the respiratory system and in the quality-of-life endpoints of emotional state and vitality of the CFQ-R (for further information, please refer to the justification of the resolution).

The appropriate comparator therapy defined by the G-BA is identical for children from 6 months to < 6 years and for patients aged 18 years and older with an *R117H* mutation in the CFTR gene[6] as well as for patients with certain gating mutations[7] (best supportive care), thus fulfilling a criterion for evidence transfer in the benefit assessment. The standards to be applied for the recognition of evidence from other patient populations will also take into account the particularities and limitations associated with the conduct of paediatric clinical trials.

With regard to the safety profile, in accordance with the statements of the EMA in the *assessment report*[5] on ivacaftor, it is not to be assumed that there are differences between the various mutations. The present benefit assessment therefore also takes into account the results of previous benefit assessments that were resolved for children under 6 years of age with CF and certain gating mutations[7]. Overall, no disadvantage of ivacaftor + BSC compared with placebo + BSC was found in the benefit assessments regarding safety.

Because there is an identical underlying genetic cause of the disease and thus a comparable pathophysiology, it is assumed that the additional benefit observed is transferable from the population of ≥ 18-year-old patients with an *R117H* mutation to the population of 6-month- to < 6-year-old children with the same mutation. Because of the uncertainties associated with this and the limitations of the available evidence, the extent of the additional benefit is non-quantifiable.

Summary:

Overall, the G-BA concludes that the transferability of the additional benefit for ivacaftor from patients aged 18 years and older to children from 6 months to < 6 years with cystic fibrosis with an *R117H* mutation in the *CFTR* gene is assumed, especially against the background of the comparable disease pattern, the progressive course, and the limitations in conducting clinical trials in this age group, taking into account the data on the safety of children with gating mutations.

However, the additional benefit is non-quantifiable because the scientific data basis does not allow it at this stage.

[6] CF patients from 18 years with *R117H* mutation with the resolution of 20 February 2020

[7] CF patients with gating mutations (*G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R*): 6 to < 12 months with the resolution of 4 June 2020; 12 to < 24 months with the resolution of 20 February 2020; 2–5 years with the resolution of 20 February

Reliability of data (probability of additional benefit)

Because of the uncertainty caused by the transfer of the additional benefit to a younger population, an overall hint is derived.

b) For patients from 6 to < 18 years of age with cystic fibrosis who have an *R117H* mutation in the *CFTR* gene, there is a hint for a non-quantifiable additional benefit.

Justification:

For the benefit assessment of ivacaftor in children aged 6 years to < 18 years with cystic fibrosis who have an *R117H* mutation in the *CFTR* gene, the pharmaceutical company submits the randomised controlled trial VX11-770-110 (hereinafter referred to as Study 110), which compared ivacaftor + BSC with placebo + BSC over a treatment period of 24 weeks. The pharmaceutical company also presents the results of study VX12-770-112 (Study 112) for patients aged < 18 years with an *R117H* mutation in the *CFTR* gene as a supplement but does not use these to derive the additional benefit.

Study 112 is an open-label, non-randomised extension study with 2 arms. The intervention arm of the study included patients who had previously received ivacaftor as an intervention in randomised controlled trial (RCT) 110 or 2 other intervention trials. There was also an observation arm (without intervention), which included patients who had received at least 4 weeks of ivacaftor and decided against being included in the ivacaftor arm in the extension study. A comparison with the appropriate comparator therapy was not carried out. Study 112 can therefore not be used for the assessment of the additional benefit in the present therapeutic indication.

RCT 110 included children ≥ 6 years, adolescents, and adults with cystic fibrosis and an *R117H* mutation in at least one allele in the *CFTR* gene. The sub-population of this study (≥ 6 to < 18 years) relevant for the present therapeutic indication comprised 20 patients. Of these, 10 patients were randomised to the intervention arm (ivacaftor) and 10 patients to the comparator arm (placebo). Only one patient aged 12 to 17 years was included per treatment group. The results presented thus essentially refer to the age group of 6–11 year old patients. Most patients included were found to have normal lung function at the start of study and showed no relevant deviation from an age- and sex-specific normal weight. The treatment with ivacaftor (150 mg every 12 hours according to the product information) or placebo was carried out in addition to the basic therapy. The study period of 24 weeks is considered an appropriate observation period for the present assessment.

From the data presented in the dossier, it appears that in the overall population of the study, patients received concomitant medication for the symptomatic treatment of cystic fibrosis, including dornase alfa, antibiotics, bronchodilators, corticosteroids, painkillers, vitamin preparations, and physiotherapy. However, there was a restriction on concomitant therapy for inhaled hypertonic saline solution. In accordance with the study protocol, this was not allowed within 4 weeks before the first intake of the study medication or had to be discontinued before the start of study. Only a protocol change shortly before the end of the study made the application possible afterwards. For the patients already included before the protocol change, it should therefore not have been possible to inhale with hypertonic saline solution. How many patients of the relevant

sub-population were included after this protocol change remains unclear. The concomitant medication used in Study 110 therefore does not represent a complete implementation of the appropriate comparator therapy, best supportive care. In addition, there is a lack of information on the concomitant therapy of the relevant sub-population as well as whether and in how many patients the concomitant treatment was adjusted. This means that overall uncertainties have to be taken into account for the assessment of the additional benefit.

As a primary endpoint of the study, the "absolute change in FEV_1%" (percentage of forced expiratory one-second volume) was surveyed. In addition, endpoints in the categories mortality, morbidity, quality of life, and side effects were surveyed. All endpoints were surveyed up to a maximum of 4 weeks after the end of treatment.

Cystic fibrosis is a progressive disease (i.e. the severity increases with age so that younger patients with cystic fibrosis show hardly any measurable symptoms). Particularly in patients with an *R117H* mutation, the manifestation of the disease can be significantly delayed so that children (and adolescents) with this mutation often show a milder course of the disease than is the case with other mutations. The present benefit assessment therefore takes into account that, because of the minor burden of symptoms, it is difficult to measure an influence of the disease course on patient-relevant endpoints, especially in children (but also adolescents) with an *R117H* mutation.

In patients aged 18 years and older with an *R117H* mutation who suffered from a higher burden of symptom in Study 110 than the patient population to be assessed here, a minor additional benefit for ivacaftor compared with BSC has already been established (see justification of the resolution of 20 February 2020). Both the symptomatology of the respiratory system and the quality-of-life endpoints emotional state and vitality of the CFQ-R showed an advantage for ivacaftor compared with the appropriate comparator therapy BSC.

The assessment report of the European Medicines Agency[8] states that the data from adults with *R117H* mutation from Study 110 were taken into account in the marketing authorisation of the new therapeutic indication for children and adolescents.

Extent and probability of the additional benefit

Mortality
No deaths occurred in Study 110.

Morbidity

Pulmonary exacerbations and hospitalisation caused by pulmonary exacerbations

Pulmonary exacerbations, above all those that lead to admission to hospital, present a clinically relevant endpoint and are to be viewed as patient-relevant.

In Study 110, no pulmonary exacerbations occurred in the relevant sub-population and consequently no hospitalisations because of pulmonary exacerbations occurred during the course of the study.

[8] Assessment report, Kalydeco, EMA/297262/2020 from 30 April 2020; available at www.ema.europa.eu/en/documents/variation-report/kalydeco-h-c-2494-ii-0082-epar-assessment-report-variation_en.pdf

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 24-week treatment period. For both absolute and relative change in the FEV_1 value over 24 weeks, there is a statistically significant difference in favour of placebo + BSC compared with ivacaftor + BSC. However, because in the age group of the present patient population the lung damage has usually not yet manifested itself to such an extent that it can be depicted sensitively enough via the FEV_1, the significance of the result is unclear.

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)

In Study 110, 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 weight problems domain is not included for children from 6 to < 12 years of age). The CFQ-R is a validated questionnaire that measures the subjective perception through the patient's eye ("patient-reported outcome, PRO"). In the sub-population relevant for the present therapeutic indication, data were collected from only one patient per study arm for patients aged 12 to < 18 years. The pharmaceutical company therefore presents evaluations only for the domains respiratory system and gastrointestinal symptoms included in the questionnaire versions for patients from 6 to 11 years.

For the respiratory system and gastrointestinal symptoms domains of the CFQ-R on symptomatology, there is no statistically significant difference between ivacaftor + BSC and placebo + BSC.

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 sex (z-scores) are preferred over absolute values.

In Study 110, there was no statistically significant difference in BMI z-score between ivacaftor + BSC and placebo + BSC.

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 110, the endpoint sweat chloride concentration was surveyed as an absolute change at Week 24. 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 accordance with the procedure for symptomatology, only domains from the version for 6- to 11-year-olds were evaluated in the dossier for health-related quality of life. This includes the domains of physical well-being, emotional state, social limitations, body image, eating disorders, and burden of therapy of the CFQ-R.

There are no statistically significant differences between treatment groups in these domains of the CFQ-R health-related quality of life.

Side effects

For the results on the overall rate of adverse events (AE), there are data on effect estimation.

For the endpoint discontinuation because of AE and serious adverse events (SAE), there was no statistically significant difference between the treatment groups. “Constipation”, the only SAE in the study, can be both an AE and an event of the underlying disease.

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

Overall assessment

For the benefit assessment of ivacaftor for the treatment of cystic fibrosis in patients aged 6 to < 18 years who have the *R117H* mutation in the *CFTR* gene, the pivotal, multi-centre, randomised, double-blind, placebo-controlled Phase III Study 110 was submitted. This study provides results on mortality, morbidity, quality of life, and side effects.

No deaths occurred in Study 110.

There were no statistically significant differences between the treatment arms for the endpoints pulmonary exacerbations, hospitalisation because of pulmonary exacerbations, the BMI z-score, and in the domains of symptomatology assessed by CFQ-R in the patient version.

Also in the category health-related quality of life in the corresponding domains of the CFQ-R as well as in the category side effects, there are no statistically significant differences between the treatment groups in the overall view. Thus neither an advantage nor a disadvantage for ivacaftor compared with BSC can be derived.

Considering that there is an identical underlying genetic cause of the disease and a comparable pathophysiology and that the expression of the symptoms becomes stronger only with increasing age, and in view of the matching appropriate comparator

therapies in both populations, the additional benefit identified in the resolution of 20 February in the population of patients aged ≥ 18 years is taken into account in the overall assessment. However, because of the associated uncertainties and the limitations of the evidence available, the extent is non-quantifiable.

Summary:

In conclusion, based on the results of Study 110, taking into account the results of patients aged 18 years and older, there is an additional benefit for ivacaftor for the treatment of cystic fibrosis in patients aged 6 to < 18 years with an *R117H* mutation in the *CFTR* gene compared with the appropriate comparator therapy. However, because of the limited evidence available, this is non-quantifiable.

Reliability of data (probability of additional benefit)

This assessment is based on the results of Study 110 in children and adolescents aged 6 to < 18 years, taking into account the assessment of ivacaftor in patients aged 18 years and older based on the same study.

In Study 110, 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, an overall hint is derived.

2.1.4 Summary of the assessment

The present assessment refers to the benefit assessment of a new therapeutic indication for the active ingredient ivacaftor. Kalydeco® was approved as an orphan drug but has exceeded the € 50 million turnover limit.

The present resolution relates to the therapeutic indication “for the treatment of patients from 6 months to < 18 years of age with cystic fibrosis who have an *R117H-CFTR* mutation”.

In the therapeutic indication to be considered, the following patient groups were distinguished:

a) Patients from 6 months to < 6 years of age with cystic fibrosis who have an *R117H* mutation in the *CFTR* gene and

b) Patients from 6 years to < 18 years of age with cystic fibrosis who have an *R117H* mutation in the *CFTR* gene.

Patient population a)

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

The pharmaceutical company does not present comparative studies and transfers the results of ivacaftor treatment in adults with R117H mutation to patients 6 months and older. It also presents results from the observational study VX15-770-122. Although

the data are not suitable for assessing the added benefit compared with the appropriate comparator therapy because of the lack of comparison with best supportive care and the descriptive evaluation, they provide supporting data for a transfer of the additional benefit.

In particular, against the background of the comparable clinical picture, the progressive course, and the limitations in the conduct of clinical trials, the G-BA concludes that the additional benefit from adults (resolution of 20 February 2020) can be transferred to children aged 6 months to < 6 years with cystic fibrosis and an *R117H* mutation, taking into account the data on the safety of children with gating mutations.

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

Patient population b)

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

For the benefit assessment, the pharmaceutical company presents the randomised controlled trial VX11-770-110, in which ivacaftor was compared with placebo in addition to BSC. Overall, neither an advantage nor a disadvantage of ivacaftor over BSC can be derived from the data of this study.

Considering the fact that the patients included still have relatively few symptoms in this age group because of their young age and the often mild disease course in the R117H mutation and that there is an identical underlying genetic cause of the disease as well as the matching appropriate comparator therapies in both populations, the results in adults with R117H mutation (resolution of 20 February 2020) are taken into account in the overall consideration. Because of the associated uncertainties and the limitations of the available evidence, a hint for a non-quantifiable additional benefit can be established.

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

The G-BA uses the following derivation of patient numbers in order to enable a consistent examination of patient numbers, taking into account the most recent resolution (4 June 2020) 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. 8,000 patients with cystic fibrosis in Germany is assumed[9].

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

This figure differs from the calculation in the dossier by the pharmaceutical company, which assumes a total population of 6,340 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 (8,042 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 20 patients in the SHI target population calculated by the pharmaceutical company is an underestimate, especially in the overall view. Calculations of the IQWiG using the following proportional values for the mutations determined by the pharmaceutical company yield 26 patients in the SHI target population.

Assuming the same age distribution as in the entire register evaluation collective, the following patient numbers result: 7 in patient population a (≥ 6 months to < 6 years) and 19 in patient population b (≥ 6 years to < 18 years).

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: 24 September 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 December 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 according to Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined based on consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on the costs per pack after deduction of the statutory rebates.

The average body measurements from the official representative statistics “Microcensus 2017 - body measurements of the population” were used to calculate the

dosages as a function of the body weight (average body weight of 7.6 kg for children under one year and 20.8 kg for 5-year-old children).[10]

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 is different for each individual patient and/or is shorter on average. The time unit “days” is used to calculate the “number of treatments/patient/year”, the time between individual treatments, and the maximum treatment duration if specified 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				
a) Patients from 6 months to < 6 years of age with cystic fibrosis who have an *R117H* mutation in the *CFTR* gene				
Ivacaftor	continuously, 2 × daily every 12 h	365	1	365
Best supportive care	different for each individual patient			
b) Patients from 6 years to < 18 years of age with cystic fibrosis who have an *R117H* mutation in the *CFTR* gene				
Ivacaftor	continuously, 2 × daily every 12 h	365	1	365

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

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Best supportive care	different for each individual patient			
Appropriate comparator therapy				
a) Patients from 6 months to < 6 years of age with cystic fibrosis who have an *R117H* mutation in the *CFTR* gene				
Best supportive care	different for each individual patient			
b) Patients from 6 years to < 18 years of age with cystic fibrosis who have an *R117H* mutation in the *CFTR* gene				
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					
a) Patients from 6 months to < 6 years of age with cystic fibrosis who have an *R117H* mutation in the *CFTR* gene					
Ivacaftor	50 mg – 75 mg	100 mg – 150 mg	2 × 50 mg – 2 × 75 mg	365	730 × 50 mg – 730 × 75 mg
Best supportive care	different for each individual patient				
b) Patients from 6 years to < 18 years of age with cystic fibrosis who have an *R117H* mutation in the *CFTR* gene					

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Ivacaftor	150 mg	300 mg	2 × 150 mg	365	730 × 150 mg
Best supportive care	different for each individual patient				
Appropriate comparator therapy					
a) Patients from 6 months to < 6 years of age with cystic fibrosis who have an *R117H* mutation in the *CFTR* gene					
Best supportive care	different for each individual patient				
b) Patients from 6 years to < 18 years of age with cystic fibrosis who have an *R117H* mutation in the *CFTR* gene					
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					
a) Patients from 6 months to < 6 years of age with cystic fibrosis who have an *R117H* mutation in the *CFTR* gene					
Ivacaftor 50 mg	56 GRA	€ 16,017.86	€ 1.77	€ 937.86	€ 15,078.23
Ivacaftor 75 mg	56 GRA	€ 16,017.86	€ 1.77	€ 937.86	€ 15,078.23
Best supportive care	different for each individual patient				
b) Patients from 6 years to < 18 years of age with cystic fibrosis who have an *R117H* mutation in the *CFTR* gene					
Ivacaftor 150 mg	56 FCT	€ 16,017.86	€ 1.77	€ 937.86	€ 15,078.23
Best supportive care	different for each individual patient				
Appropriate comparator therapy					
a) Patients from 6 months to < 6 years of age with cystic fibrosis who have an *R117H* mutation in the *CFTR* gene					
Best supportive care	different for each individual patient				
b) Patients from 6 years to < 18 years of age with cystic fibrosis who have an *R117H* mutation in the *CFTR* gene					
Best supportive care	different for each individual patient				
Abbreviations: GRA: granules in sachets; FCT: film-coated tablets					

Pharmaceutical selling price (LAUER-TAXE®) as last revised: 1 December 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 assessed 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

At its session on 23 June 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 25 June 2020, the pharmaceutical company submitted a dossier for the benefit assessment of ivacaftor to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, Number 2 VerfO.

By letter dated 25 June 2020 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient ivacaftor.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 September 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 1 October 2020. The deadline for submitting written statements was 22 October 2020.

The oral hearing was held on 9 November 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 8 December 2020, and the proposed resolution was approved.

At its session on 17 December 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	23 June 2020	Determination of the appropriate comparator therapy
Working group Section 35a	4 November 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	9 November 2020	Conduct of the oral hearing
Working group Section 35a	18 November 2020 2 December 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	8 December 2020	Concluding discussion of the draft resolution
Plenum	17 December 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 17 December 2020

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

Prof. Hecken