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 Tezacaftor/Ivacaftor (Reassessment of an Orphan Drug after the € 50 Million Turnover Limit Was Exceeded: Cystic Fibrosis, Combination Regimen with Ivacaftor in Patients over 12 Years of Age (Homozygous with Respect to F508del))

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 combination tezacaftor/ivacaftor (Symkevi) was listed for the first time on 1 December 2018 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices. Symkevi 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 16 May 2019, the G-BA passed a resolution on the benefit assessment of the active ingredient combination tezacaftor/ivacaftor in therapeutic indication “Symkevi is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation” 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 according to Section 5, paragraph 1 through 6 demonstrating the additional benefit compared with the appropriate comparator therapy.

In a letter dated 4 March 2020, the pharmaceutical company was requested to submit a dossier for a benefit assessment according to Section 35a SGB V by 1 July 2020 because the € 50 million turnover limit had been exceeded between December 2018 and November 2019. 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 26 June 2020.

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 tezacaftor/ivacaftor compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment (A20-54) 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 IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of tezacaftor/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 tezacaftor/ivacaftor (Symkevi) in accordance with the product information

Symkevi is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who are heterozygous for the F508del mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G and 3849+10kbC→T.

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

Symkevi is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Patients older than 12 years of age with cystic fibrosis and who are homozygous for the F508del mutation.

Lumacaftor/ivacaftor (LUM/IVA)

[1] General Methods, Version 6.0 dated 5 November 2020. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), Cologne.

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 therapy of CF:

For the patient group to be considered in the present therapeutic indication “patients 12 years of age and older with cystic fibrosis who are homozygous for the F508del mutation” the active ingredient combination lumacaftor/ivacaftor (CFTR modulators) is approved.

The following medicinal products are additionally approved for the symptomatic treatment of CF:

Aztreonam, carbocisteine[2], ceftazidim, ciprofloxacin, colistimethate, dornase alfa, levofloxacin[3], meronem, mannitol, 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 12 years of age and older with cystic fibrosis who are homozygous for the F508del mutation”, the G-BA has passed the following resolutions:

- For ivacaftor as a combination regimen with tezacaftor/ivacaftor, no additional benefit was identified for the patient group “patients aged 12 years and older” (resolution of 20 February 2020)
- For LUM/IVA, an indication for a considerable additional benefit was identified for the patient group “patients aged 12 years and older” (resolution of 2 June 2016).

For patients who are homozygous for the F508del mutation in the CFTR gene, the following further resolutions of the G-BA regarding a modification of the AM-RL are pending: Annex XII – Resolutions on the Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V:

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

- For LUM/IVA, a non-quantifiable additional benefit was determined for the patient group “children aged 2 years to 5 years” (resolution of 15 August 2019).
- For LUM/IVA there is a hint for a non-quantifiable additional benefit for the patient group “children from 6 to 11 years of age” (resolution of 2 August 2018).

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 12 years and older with CF who are homozygous for the F508del mutation in the CFTR gene, the aforementioned medicinal and non-medicinal therapy options are available. In the present evidence, medicinal therapy with LUM/IVA is recommended. In the present indication, LUM/IVA is therefore determined as an appropriate comparator therapy.

Patients should also be provided with symptomatic therapy with the aforementioned medicinal and non-medicinal therapy options insofar as these are indicated. 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).

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 tezacaftor/ivacaftor in combination with ivacaftor (TEZ/IVA + IVA) has been assessed as follows:

<u>Patients older than 12 years of age with cystic fibrosis and who are homozygous for the F508del mutation.</u>

An additional benefit is not proven.

Justification:

For the assessment of the additional benefit of TEZ/IVA + IVA in patients over 12 years of age with cystic fibrosis who are homozygous for the F508del mutation in the CFTR gene, an indirect comparison between TEZ/IVA + IVA and lumacaftor/ivacaftor (LUM/IVA) was presented by the pharmaceutical company. This was based on a total of three RCTs: Study 106 (TEZ/IVA + IVA+ BSC vs placebo + BSC), Study VX12-809-103 (LUM/IVA + BSC vs placebo + BSC), and Study VX12-809-104 (LUM/IVA + BSC vs placebo + BSC) with placebo as bridge comparator. In both arms of Studies 106, 103, and 104, the patients additionally received the best-possible symptomatic therapy (BSC).

The data presented in the dossier shows that the patients received a comprehensive symptomatic medicinal therapy, including dornase alfa, sodium chloride, pancreatin, and salbutamol as well as antibiotics, dietary supplements, and corticosteroids at the time of study inclusion and during the course of Studies 106, 103 and 104. Overall, it is to be assumed that at least one appropriate (stable) basic therapy with mucolytics and pancreas enzymes was carried out.

The pivotal Study VX14-661-106 (hereinafter referred to as Study 106) is a multi-centre, randomised, double-blind, placebo-controlled Phase III parallel group study. The patients in Study 106 were randomised in a 1:1 ratio to the intervention arm (TEZ/IVA + IVA + BSC; N = 251) or the comparator arm (placebo + BSC; N = 259) randomised, stratified by age (< 18 years vs ≥ 18 years), sex (male vs female) and FEV_1 (< 70% vs ≥ 70%).

Study 106 included patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene and who had a confirmed diagnosis of cystic fibrosis defined as a sweat chloride value ≥ 60 mmol/l. The patients included had to have an FEV_1 of ≥ 40% and ≤ 90% of the standard value for age, sex, and height at the time of screening. Patients who had already been treated with LUM/IVA were excluded from the study population. In Study 106, the dosage of TEZ/IVA and IVA followed the specifications in the product information.

Studies VX12-809-103 and VX12-809-104 (hereinafter referred to as Studies 103 and 104) are randomised, double-blind, placebo-controlled parallel group Phase III studies. In Study 103 and 104, 559 and 563 patients, respectively were included and randomised to the following study arms at a ratio of 1:1:1: LUM (600 mg, once daily)/IVA (250 mg, every 12 hours), LUM (400 mg, every 12 hours)/ IVA (250 mg, every 12 hours), and placebo. The intervention LUM (600 mg, once daily)/IVA, which is not compliant with marketing authorisation, is not relevant for the benefit assessment. In Study 103, 185 vs 187 vs 187 patients were included in each of the three treatment arms. In Study 104, 187 vs 189 vs 187 patients were included in the treatment arms.

Except for the definition of the confirmed diagnosis of cystic fibrosis, the inclusion and exclusion criteria of the studies are largely comparable to the criteria described for Study 106. In Studies 103 and 104, cystic fibrosis was defined as a sweat chloride level of ≥ 60 mmol/l or two cystic fibrosis-causing mutations and one chronic sinopulmonary disease or gastrointestinal/nutritional abnormalities. In both studies, the stratification factors were identical to those in Study 106: Age (< 18 years / ≥ 18 years), sex (male/female), the FEV_1 as a percentage of the standardised normal value (< 70%/≥ 70%).

As a primary endpoint of Studies 106, 103, and 104, 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.

In Studies, 106, 103, and 104, the treatment duration was 24 weeks.

The single-arm, open-label Phase III extension study, VX14-661-110 (hereinafter referred to as Study 110; TEZ/IVA + IVA) with a data cut-off at Week 96 was also submitted by the pharmaceutical company. Patients with the homozygous (Studies VX13-661-103, VX14-661-106, VX14-661-111) as well as the heterozygous F508del mutation (Studies VX14-661-107, VX14-661-108, VX14-661-109) in the CFTR gene were included in the study. Study 110 is not considered for the present benefit assessment because of the lack of a control group.

Extent and probability of the additional benefit

Mortality

No deaths occurred in Studies 106, 103, and 104.

Morbidity

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 in Studies 106, 103, and 104 as an absolute change over a 24-week treatment period. In the adjusted indirect comparison, a statistically significant difference was found for the FEV_1% in favour of TEZ/IVA + IVA compared with LUM/IVA.

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

Sweat chloride concentration (mmol/l)

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

The endpoint sweat chloride concentration was recorded only in Study 106. In Studies 103 and 104, this endpoint was not collected. Thus, no adjusted indirect comparison with LUM/IVA via the bridge comparator placebo was possible based on the data available.

Pulmonary exacerbations, hospitalisation and i.v. antibiotics therapy based on 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.

For the endpoint pulmonary exacerbations, the adjusted indirect comparison of the frequency of pulmonary exacerbations operationalised as event rate per year showed no statistically significant difference between the treatment groups.

For the endpoint hospitalisation caused by pulmonary exacerbations, the adjusted indirect comparison based on the event rate per year showed a statistically significant disadvantage of TEZ/IVA + IVA compared with LUM/IVA.

However, the results of the present adjusted indirect comparison are subject to considerable uncertainties for this endpoint. The bridge comparator for the adjusted indirect comparison of Study 106 (TEZ/IVA + IVA vs placebo) as well as Studies 103 (LUM/IVA vs placebo) and 104 (LUM/IVA vs placebo) is placebo. The number of events per patient year in the placebo arm of Study 106 (TEZ/IVA + IVA vs placebo) is significantly lower (0.28) than in the two placebo arms of the LUM/IVA studies (Study 103: 0.54; Study 104: 0.69). In contrast, the number of pulmonary exacerbations leading to hospitalisation in the respective verum arms is of a comparable magnitude in the three studies: Study 106 (TEZ/IVA + IVA vs placebo): 0.23; Study 103 (LUM/IVA vs placebo): 0.21, and Study 104 (LUM/IVA vs placebo): 0.27 per patient year.

In addition, there are clear imbalances between Study 106 and Studies 103/104 regarding the baseline parameter “region”. In Study 106, the majority of patients were from Europe, whilst in Studies 103/104, the majority of patients were from the USA. Especially against the background that the conditions of hospitalisation depend on the design of the respective health care system, the results cannot be interpreted with any degree of significance.

Because of these considerable uncertainties and the result that the overall rate for the endpoint pulmonary exacerbations showed no statistically significant difference between the treatment groups, the statistically significant disadvantage of TEZ/IVA + IVA compared with LUM/IVA for the endpoint hospitalisation because of pulmonary exacerbations does not lead to a derivation of a lesser benefit of TEZ/IVA + IVA in the assessment of the G-BA.

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.

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 and weight problems as well as the gastrointestinal domain. 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 caregiver.

For the respiratory system domain, a statistically significant advantage of TEZ/IVA + IVA compared with LUM/IVA was found for the patient version in the indirect adjusted comparison. The 95% confidence interval of the Hedges' g in this case does not lie fully outside of the irrelevance range. The clinical relevance of the effect observed in the mean difference can therefore not be assessed.

For the domains of the CFQ-R domain weight problems as well as for the gastrointestinal domain, the pharmaceutical company exclusively submits the standardised mean difference (SMD) in the form of Hedges' g. For the domain weight problems as well as for the gastrointestinal domain, no statistically significant difference between the treatment groups was shown.

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 Studies 106, 103, and 104, the endpoint absolute change in BMI z-score was established for patients under 20 years of age. For the endpoint absolute change in the BMI z-score, the adjusted indirect comparison showed a statistically significant difference to the detriment of TEZ/IVA + IVA compared with LUM/IVA; however, the extent of this cannot be conclusively assessed.

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.

For the individual domains of the CFQ-R, the pharmaceutical company exclusively submits the standardised mean difference (SMD) in the form of Hedges' g.

For the patient version, a statistically significant difference in favour of TEZ/IVA + IVA compared with LUM/IVA was found for the domain burden of therapy in the adjusted indirect comparison. The 95% confidence interval of the Hedges' g in this case does not lie fully outside of the irrelevance range. The clinical relevance of the effect observed can therefore not be assessed.

For the domains of physical well-being, emotional state, vitality, social limitations, role functioning, body image, eating disorders, and subjective perception of health, no statistically significant differences were found between the treatment groups in the adjusted indirect comparison.

Side effects

For the endpoint SAEs, the pharmaceutical company submitted evaluations minus the preferred term (PT) infectious pulmonary exacerbations attributable to the underlying disease cystic fibrosis. As a result of the evaluations of the SAEs submitted later by the pharmaceutical company, most of the events that can be assigned to the underlying disease are not included in the evaluations.

The effect estimate for the indirect comparison for the endpoints SAEs and therapy discontinuations because of AEs is not sufficiently reliable. A higher or lower harm from TEZ/IVA + IVA compared with LUM/IVA is thus not proven in each case.

For the specific AEs, a statistically significant advantage of TEZ/IVA + IVA compared with LUM/IVA was found for the endpoint rash (PT) in the adjusted indirect comparison.

In the side effects category, there are no clinically relevant differences between TEZ/IVA + IVA compared with LUM/IVA.

Overall assessment/conclusion

For the benefit assessment of TEZ/IVA + IVA for the treatment of cystic fibrosis (CF, cystic fibrosis) in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene, an indirect comparison between TEZ/IVA + IVA and lumacaftor/ivacaftor (LUM/IVA) was used. This was based on a total of three RCTs: Study 106 (TEZ/IVA + IVA + BSC vs placebo + BSC), Study 103 (LUM/IVA + BSC vs placebo + BSC), and Study 104 (LUM/IVA + BSC vs placebo + BSC) with placebo as bridge comparator. The indirect adjusted comparison yields results on mortality, morbidity, quality of life, and side effects.

No deaths occurred in Studies 106, 103, and 104.

In the morbidity category, the adjusted indirect comparison for the endpoint pulmonary exacerbations showed no statistically significant difference between the treatment groups.

For the endpoint hospitalisation caused by pulmonary exacerbations, the adjusted indirect comparison showed a statistically significant disadvantage of TEZ/IVA + IVA compared with LUM/IVA.

However, because of existing uncertainties regarding possible regional differences in hospitalisation and because no statistically significant difference between the treatment groups was found in the overall rate for the endpoint pulmonary exacerbations, the disadvantage of TEZ/IVA + IVA compared with LUM/IVA identified for the endpoint hospitalisation caused by pulmonary exacerbations does not lead to a derivation of a lesser benefit of TEZ/IVA + IVA in the assessment of the G-BA.

For the respiratory system domain of the CFQ-R, a statistically significant advantage of TEZ/IVA + IVA compared with LUM/IVA was found for the patient version in the indirect adjusted comparison, although the clinical relevance cannot be assessed.

For the weight problems domain as well as for the gastrointestinal domain of the CFQ-R, no statistically significant difference between the treatment groups was shown.

For the endpoint absolute change in the BMI z-score, the adjusted indirect comparison showed a statistically significant difference to the detriment of TEZ/IVA + IVA compared with LUM/IVA; however, the extent of this cannot be conclusively assessed.

In the summary of the results on morbidity, there is no relevant difference between TEZ/IVA + IVA and LUM/IVA for the benefit assessment.

In the quality of life and side effects categories, there are no clinically relevant differences between TEZ/IVA + IVA and LUM/IVA.

In summary, for patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene, there is no additional benefit for TEZ/IVA + IVA compared with LUM/IVA in the overall consideration of the results on mortality, morbidity, quality of life, and side effects.

2.1.4 Summary of the assessment

The present assessment is the renewed benefit assessment (because the € 50 million turnover limit was exceeded) of the active ingredient combination tezacaftor/ivacaftor (TEZ/IVA) in combination with ivacaftor (IVA). The present assessment refers to the therapeutic indication “for the treatment of patients 12 years of age and older with cystic fibrosis who are homozygous for the F508del mutation”.

Tezacaftor/ivacaftor has received marketing authorisation as an orphan drug.

Lumacaftor/ivacaftor (LUM/IVA) was determined as an appropriate comparator therapy by the G-BA.

For the benefit assessment of TEZ/IVA + IVA for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene, an indirect comparison between TEZ/IVA + IVA and LUM/IVA was used. This was based on a total of three RCTs: Study 106 (TEZ/IVA + IVA + BSC vs placebo + BSC), Study 103 (LUM/IVA + BSC vs placebo + BSC), and Study 104 (LUM/IVA + BSC vs placebo + BSC) with placebo as bridge comparator. The indirect adjusted comparison yields results on mortality, morbidity, quality of life, and side effects.

No deaths occurred in Studies 106, 103, and 104.

In the morbidity category, the adjusted indirect comparison for the endpoint pulmonary exacerbations showed no statistically significant difference between the treatment groups.

For the endpoint hospitalisation caused by pulmonary exacerbations, the adjusted indirect comparison showed a statistically significant disadvantage of TEZ/IVA + IVA compared with LUM/IVA.

However, because of existing uncertainties regarding possible regional differences in hospitalisation and because no statistically significant difference between the treatment groups was found in the overall rate for the endpoint pulmonary exacerbations, the disadvantage of TEZ/IVA + IVA compared with LUM/IVA identified for the endpoint hospitalisation caused by pulmonary exacerbations does not lead to a derivation of a lesser benefit of TEZ/IVA + IVA in the assessment of the G-BA.

For the respiratory system domain of the CFQ-R, a statistically significant advantage of TEZ/IVA + IVA compared with LUM/IVA was found for the patient version in the indirect adjusted comparison, although the clinical relevance cannot be assessed.

For the weight problems domain as well as for the gastrointestinal domain of the CFQ-R, no statistically significant difference between the treatment groups was shown.

For the endpoint absolute change in the BMI z-score, the adjusted indirect comparison showed a statistically significant difference to the detriment of TEZ/IVA + IVA compared with LUM/IVA; however, the extent of this cannot be conclusively assessed.

In the summary of the results on morbidity, there is no relevant difference between TEZ/IVA + IVA and LUM/IVA for the benefit assessment.

In the quality of life and side effects categories, there are no clinically relevant differences between TEZ/IVA + IVA and LUM/IVA.

In summary, for patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene, there is no additional benefit for TEZ/IVA + IVA compared with LUM/IVA in the overall consideration of the results on mortality, morbidity, quality of life, and side effects.

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

Patients older than 12 years of age with cystic fibrosis and who are homozygous for the F508del mutation.

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 (20 February 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[4].

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).

1. The percentage of patients with confirmed homozygous F508del mutation in the CFTR gene is 46.4%[5] (3,712 patients).
2. The percentage of patients 12 years of age and older in the entire patient group is approx. 73.1% [5] (2,713 patients).
3. Taking into account that 87.86% of patients are covered by statutory health insurance (SHI), there are 2,384 patients in the target population.

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 Symkevi (active ingredient combination: tezacaftor/ivacaftor) at the following publicly accessible link (last access: 28 October 2020): https://www.ema.europa.eu/documents/product-information/symkevi-epar-product-information_de.pdf

Treatment with tezacaftor/ivacaftor may be initiated and monitored only 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).

Treatment duration:

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.

[4] https://www.muko.info/ (https://www.muko.info/englisch-version/) Website of Mukoviszidose e.V. (German Cystic Fibrosis Association) [accessed 27 June 2019]
[5] Nährlich L, Burkhart M, Wosniok J. German Cystic Fibrosis Registry: Annual Report 2018. 2019 https://www.muko.info/fileadmin/user_upload/angebote/qualitaetsmanagement/register/berichtsbaende/berichtsband_2018.pdf.

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Tezacaftor/ ivacaftor	continuously, 1 × daily	365	1	365
Ivacaftor	continuously, 1 × daily	365	1	365
Appropriate comparator therapy				
Lumacaftor/ ivacaftor	continuously, 2 × daily every 12 h	365	1	365

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					
Tezacaftor/ ivacaftor	100 mg/150 mg	100 mg/150 mg	1 × 100 mg/150 mg	365	365 × 100 mg/150 mg
Ivacaftor	150 mg	150 mg	1 × 150 mg	365	365 × 150 mg
Appropriate comparator therapy					
Lumacaftor/ ivacaftor	400 mg/250 mg	800 mg/500 mg	4 × 200 mg/125 mg	365	1,460 × 200 mg/125 mg

Costs:

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.

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					
Tezacaftor/ivacaftor	28 FCT	€ 6,243.43	€ 1.77	€ 365.20	€ 5,876.46
Ivacaftor	56 FCT	€ 16,017.86	€ 1.77	€ 937.86	€ 15,078.23
Appropriate comparator therapy					
Lumacaftor/ivacaftor	112 FCT	€ 11,771.75	€ 1.77	€ 689.09	€ 11,080.89
Abbreviations: 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 10 March 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 26 June 2020, the pharmaceutical company submitted a dossier for the benefit assessment of tezacaftor/ivacaftor to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, Number 6 VerfO.

By letter dated 29 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 combination tezacaftor/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	10 March 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