# Justification

Gemeinsamer Bundesausschuss

## to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Appendix XII – Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V Tezacaftor/ivacaftor

From 16. May 2019

**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.

For medicinal products for the treatment of a rare disease (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999, according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional medicinal benefit is deemed to be proven through the grant of the marketing authorisation. Evidence of the medicinal benefit and the additional medicinal benefit in relation to the appropriate comparator therapy need not be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, Nos. 2 and 3 SGB V in conjunction with the 5th Chapter, Sections 5 et seq. of the Rules of Procedure, G-BA (VerfO) has not been carried out. Only the extent of the additional benefit has to be demonstrated.

However, the restricted benefit assessments for orphan drugs as linked by law to marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices including VAT exceeds €50 million in the last 12 calendar months. According to Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical manufacturer must, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, subsection 1–6 VerfO, in particular regarding the additional medicinal benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO. In this dossier, the pharmaceutical manufacturer must also provide evidence of the additional benefit in relation to the appropriate comparative therapy.

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG; Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen). On the basis of the statutory requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is deemed to have been proven through the grant of marketing authorisation, the G-BA modified the procedure for the benefit assessment of orphan drugs at its meeting on 15 March 2012 to the effect that, in the case of orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit provided by the G-BA is evaluated exclusively on the basis of the approval studies.

Accordingly, at its meeting on 15 March 2012, the G-BA amended the mandate given to IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V in such a way that, in the case of orphan drugs, IQWiG is only commissioned to carry out a benefit assessment in case of a previously defined comparator therapy when the sales volume of the drug concerned has exceeded the legal limit of € 50 million and is therefore subject to an unrestricted benefit assessment (cf. Section 35a, paragraph 1, sentence 12 SGB V). According to Section 35a, paragraph 2 SGB V, the assessment by the G-BA 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 shall decide 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 relevant date for the first placement on the (German) market of the active ingredient Tezacaftor/ivacaftor in accordance with Chapter 5, Section 8, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is the 1. Dezember 2018. The pharmaceutical manufacturer submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) on 5. November 2018.

Tezacaftor/ivacaftor for the treatment of cystic fibrosis is authorised 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.

According to Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be already proven. The extent of the additional benefit is assessed on the basis of the approval studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical manufacturer in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 1. März 2019 together with the IQWiG assessment on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. Furthermore, an oral hearing was held.

The G-BA has made its resolution on the basis of the dossier of the pharmaceutical manufacturer, the dossier evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G18-20), prepared by the IQWiG, and the statements submitted in the written and oral hearing procedures.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for approval with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by IQWiG in accordance with the General Methods [1]was not used in the benefit assessment ofTezacaftor/ivacaftor.

In light of the above, and taking into account the statements received as well as the oral hearing, the G-BA has arrived at the following assessment:

### 2.1 Additional benefit of the medicinal product

#### 2.1.1 Approved therapeutic indication of Tezacaftor/ivacaftor (Symkevi®) in accordance with the product information

Symkevi® is used with ivacaftor 150 mg tablets establishing treatment of cystic fibrosis (CF) in patients 12 years of age and older who display homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation and one of the following mutations in the CFTR gene (Cystic Fibrosis Trans-membrane Conductance Regulator): P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G and 3849+10kbC→T.

#### 2.1.2 Extent of the additional benefit

In summary, the additional benefit of Tezacaftor/ivacaftor have been assessed as follows:

a) For patients 12 years of age and older with cystic fibrosis and who are homozygous for the *F508del* mutation, there is a considerable additional benefit for TEZ/IVA.

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.

Rationale:

For the assessment of the additional benefit of TEZ/IVA in patients 12 years and older with cystic fibrosis and who are homozygous for the *F508del* mutation in the CFTR gene, the Phase III VX14-661-106 (Study 106 henceforth) multi-centre, randomised, double-blind, placebo-controlled parallel group study justifying the marketing authorisation was submitted by the pharmaceutical manufacturer.

The patients in Study 106 were randomised in a 1:1 ratio to the intervention arm (TEZ/IVA; N=251) or the comparative arm (placebo; N=259) randomised, stratified according to age (< 18 years vs. ≥ 18 years), gender (male vs. female) and $FEV_1$ (< 70% vs. ≥ 70%). The enrolled patients from 12 years and older i with a confirmed CF diagnosis and a homozygous *F508del* mutation in the CFTR gene needed to display an $FEV_1$ ranging from ≥ 40% to ≤ 90% of the standard values for age, gender and physique at the time of the screening. Patients with severely impaired liver function as well as patients who had already been treated with LUM/IVA were excluded from the study population.

The data presented in the dossier shows that the patients enrolled in the study received comprehensive symptomatic medical treatment during the course of the study containing among others: dornase alfa, sodium chloride, pancreatin and salbutamol as well as antibiotics, food supplements and corticosteroids. Overall, it is to be assumed that at least one appropriate (stable) basic therapy with mucolytics and pancreas enzymes took place.

As a primary endpoint in Study 106, the “absolute change in $FEV_1$%” (percentage of forced expiratory one-second volume) was levied. In addition, endpoints in the categories mortality, morbidity, quality of life as well as side effects were levied.

The treatment duration lasted 24 weeks. The dosage of TEZ/IVA and IVA followed the specifications in the product information. After the 24-week treatment period, there was a four-week safety follow-up. For patients enrolled in the Extension Study VX14-661-110, the safety follow-up was omitted.

In the hearing procedure, data on Endpoint SF-12 was presented in addition to the information already submitted in the category Health-Related Quality of Life in Study 106. On additional endpoints in the category Morbidity, further incomplete data was submitted (Pittsburgh Sleep Quality Index (PSQI), Cystic Fibrosis Respiratory Symptom Diary- Chronic Respiratory Infection Symptom Score (CFRSD-CRISS)) that were not taken in consideration in the benefit assessment.

The pharmaceutical manufacturer furthermore submitted the supportive, current, open Extension Study of Phase III VX14-661-110. 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 enrolled in the study. The study could not be taken into consideration in the benefit assessment due to its very low significance and the joint representation of results on its safety without considering the respective original study.

In addition, the pharmaceutical manufacturer had submitted an indirect comparison between TEZ/IVA and lumacaftor/ivacaftor (LUM/IVA). This was based on a total of three RCTs: Study 106 (TEZ/IVA vs. placebo), Study VX12-809-103 (LUM/IVA vs. placebo) and Study VX12-809-104 (LUM/IVA vs. placebo) with placebo as a bridge comparator. In both arms of the study, the patients in addition received the best-possible symptomatic therapy (BSC).

Based on the prevalence of fundamental higher value evidence (RCT) and in consideration of procedural provisions in the case of the benefit assessments for orphan drugs, the indirect comparison to LUM/IVA benefit assessment was not considered in the benefit assessment.

Mortality

No deaths occurred in Study 106.

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 as an absolute change over a 24-week treatment period. The absolute change in $FEV_1$% compared to Week 24 amounted to an average of +3.60% in the TEZ/IVA arm and -1.47% in the control arm of Study 106. In Study 106, a statistically significant difference for the $FEV_1$% in favour of TEZ/IVA compared to placebo was determined (MD [95% CI]: 4.79 [3.58; 6.00]; $p < 0.0001$).

Different opinions on patient relevance to $FEV_1$% exist. The overall assessment on the extent of the additional benefit remains untouched by them.

*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, there was a statistically significant benefit between TEZ/IVA to placebo in the period up to the first event (HR [95% CI]: 0.64 [0.46; 0.88]; p=0.0069) as well as in the frequency of pulmonary exacerbations operationalised as rate of events per year (rate ratio [95% CI]: 0.65 [0.48; 0.88]; p=0.0054) a statistically significant benefit of TEZ/IVA compared to placebo.

For the endpoint hospitalisations due to pulmonary exacerbations, no statistically significant difference between TEZ/IVA and placebo was shown.

The endpoint i.v. antibiotics therapy due to 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. In addition, the endpoint does not supply any further information on the endpoint hospitalisations due to pulmonary exacerbations.

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

The endpoint symptoms were recorded using the hospital-specific CFQ-R (patient version) and comprised the domains respiratory system, weight problems as well as gastrointestinal domains. The CFQ-R is a questionnaire that measures the subjective perception through the patient's eye (so-called "patient-reported outcome, PRO"), i.e. his or her evaluation through the parents or guardian.

In the patient version for the domain respiratory system, a statistically significant benefit in favour of TEZ/IVA in comparison to placebo, an improvement by ≥ 4 points was determined in the responder assessment (RR [95% CI]): 1.44 [1.16; 1.78]; p=0.0009).

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 serves to evaluate a patient's body weight in relation to his or her physique. The BMI z-score serves as a standardised measure to adjust the BMI according to the patient's age and gender. The BMI endpoint is seen as an important parameter in evaluating development disorders in paediatric patients with cystic fibrosis.

For the endpoints absolute change in BMI and absolute change in BMI z-score, the results of Study 106 did not display any statistically significant differences between the TEZ/IVA arm and the control arm.

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 patient version, the following values were determined for each domain compared to placebo: physical well-being(MD [95% CI]: 3.85 [1.88; 5.82]; p=0.0001), vitality (MD [95% CI]: 2.30 [0.10; 4.49]; p= 0.0401), subjective perception of health (MD [95% CI]: 3.20 [1.15; 5.24]; p=0.0022), burden of therapy (MD [95% CI]: 3.37 [1.65; 5.10]; p=0.0001), as well as for the domain social limitations (MD [95% CI]: 1.52 [0.03; 3.01]; p=0.0452) . The 95% confidence interval of the Hedge's g does not lie fully outside of the irrelevant range of –0.2 to 0.2 so that it is not possible to derive whether the effects observed in the mean value differences are clinically relevant.

For the domains emotional state, self-perception, eating disorders and role functions, no statistically significant differences between the treatment groups were determined.

*Health-related quality of life measured through SF-12*

The SF-12 questionnaire consists of a physical domain (PCS) and a mental domain (MCS) whereby higher sum values characterise a better health condition.

For the domain PCS, a statistically significant benefit for TEZ/IVA compared to placebo (MD [95%-CI] was shown: 1.5 [0.46; 2.54]; p=0.005). The 95% confidence interval of the Hedges' g in this case does not lie fully outside of the irrelevant range of –0.2 to 0.2 so that it is not possible to derive whether this effect is clinically relevant. For the domain MCS, no statistically significant difference between the treatment groups could be determined.

Side effects

In Study 106, for the endpoints serious adverse events (SAE) and adverse events (AE ≥ Grade 3), no statistically significant differences were shown between the TEZ/IVA arm and the control arm.

For the endpoint withdrawal due to AEs, no statistically significant difference between TEZ/IVA and placebo was shown.

For the most frequent adverse events at the SOC and PT level (with a cut-off at ≥ 10% incidence in one of the study arms): Infections and parasitic diseases (SOC), especially infectious pulmonary exacerbations of the CF (PT) and nasopharyngitis (PT), respiratory, thoracic and mediastinal disorders (SOC), especially coughing (PT), increased phlegm (PT), haemoptysis (PT) and pain in the mouth or throat (PT), gastrointestinal disorders (SOC), general disorders and administration site conditions (SOC), especially pyrexia (PT) and fatigue (PT), nervous system disorders (SOC), especially headaches (PT), investigations (SOC), musculoskeletal and connective tissue disorders (SOC) as well as skin and

subcutaneous tissue disorders (SOC). No differences were shown between the treatment arms of Study 106.

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

Overall assessment/conclusion

The randomised, double-blind, placebo-controlled phase III Study 106 was submitted for the benefit assessment on TEZ/IVA establishing treatment of cystic fibrosis (CF, mucoviscidosis) in patients 12 years of age and older who display homozygous for the *F508del* mutation in the CFTR gene. The results on mortality, morbidity, quality of life as well as side effects were yielded from Study 106.

No deaths occurred in Study 106.

Endpoints for the morbidity category were recorded as the percentage of forced expiratory volume per second ($FEV_1$ %); the symptoms were measured using CFQ-R, pulmonary exacerbations, hospitalisation and the i.v. antibiotics therapy based on pulmonary exacerbations, the BMI and the BMI z-score. Study 106 resulted in a statistically significant difference in favour of TEZ/IVA compared to the control group for the endpoint pulmonary exacerbations in the category morbidity. In the domain respiratory system of the CFQ-R, a statistically significant and clinically relevant benefit for TEZ/IVA compared to the control group was shown.

For the endpoints hospitalisations due to pulmonary exacerbations as well as BMI and BMI z-score, no statistically significant differences between the treatment arms were determined.

In the category health-related quality of life, the endpoints CFQ-R and data SF-12 were recorded in Study 106. For the endpoint CFQ-R, the domains physical well-being, vitality, subjective perception of health burden of therapy and social limitations in each case showed statistically significant differences in favour of TEZ/IVA compared to placebo, whereby the clinical relevance of each of these statistically significant improvements cannot be assessed.

For the endpoint SF-12, the domain PCS showed a statistically significant benefit for TEZ/IVA compared to placebo, whereby the clinical relevance of this statistically significant improvement cannot be assessed. For the domain MCS, no statistically significant difference between the treatment groups could be determined.

In the category side effects, there were no statistically significant differences determined between the treatment arms TEZ/IVA and placebo.

In the overall view, there are considerable additional benefit as a result.

Based on the criteria in Section 5, Paragraph 7 of the AM-NutzenV, the G-BA arrived at the following result taking the disease's degree of severity, the written statements and the oral hearing for patients 12 years of age and older with cystic fibrosis and who were homozygous for the *F508del* mutation and determined a considerable additional benefit for the treatment with TEZ/IVA.

b) For patients 12 years of age and older with cystic fibrosis, who are heterozygous for the *F508del* mutation and who display one of the following mutations in the 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: there were minor additional benefit for TEZ/IVA.

Rationale:

For the evaluation of additional benefit of TEZ/IVA in treating patients 12 years of age and older with cystic fibrosis and who are heterozygous for the *F508del* mutation in the CFTR gene and who display a mutation with the reduction function of the CFTR (RF mutation), the Phase III VX14-661-108 (Study 108 henceforth) multi-centre, randomised, double-blind, placebo-controlled cross-over study justifying the marketing authorisation was submitted by the pharmaceutical manufacturer.

The patients in Study 108 were distributed randomly in six groups. For the benefit assessment, the non-compliant intervention (IVA) is not relevant. Of a total of 248 patients, 167 patients were randomised to the intervention arm (TEZ/IVA) and 165 patients to the comparative (placebo) arm of the study in one of two treatment periods. The dosage of TEZ/IVA and IVA followed the specifications in the product information.

The stratification was based on age (< 18 years vs. ≥ 18 years), $FEV_1$ (< 70% vs. ≥ 70%) and type of RF mutation. The enrolled patients 12 years of age and older with a confirmed CF diagnosis and a heterozygous *F508del* mutation in the CFTR gene needed to display an $FEV_1$ ranging from ≥ 40% to ≤ 90% of the standard values for age, gender and physique at the time of the screening. Patients with severely limited liver function were excluded from the study.

The data presented in the dossier shows that the patients enrolled in the study received comprehensive symptomatic medical treatment during the course of the study containing among others: dornase alfa, sodium chloride, pancreatin and salbutamol as well as antibiotics, food supplements and corticosteroids. Overall, it is to be assumed that at least one appropriate (stable) basic therapy with mucolytics and pancreas enzymes took place.

As a primary endpoint in Study 108, the "absolute change in $FEV_1$%" (percentage of forced expiratory one-second volume) was levied. In addition, endpoints in the categories mortality, morbidity, quality of life as well as side effects were levied.

The Study comprised an 8-week treatment period with a subsequent cross-over to an additional 8-week treatment period. The wash-out period between the treatment periods was eight weeks. After the two treatment periods, there was a four-week safety follow-up. For patients enrolled in the Extension Study VX14-661-110, the safety follow-up was omitted.

The mere 8-week treatment phase was viewed as sufficient for the marketing authorisation to display the effectiveness, i.e. the efficacy of TEZ/IVA in the patient population. It must be taken into consideration, however, that the study duration chosen by the pharmaceutical manufacturer was too short to assess the sustainability of the effects on the patient-relevant endpoints in line with the benefit assessment and the underlying chronic disease.

The pharmaceutical manufacturer furthermore submitted the supportive, current, open extension study of phase III VX14-661-110. 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 enrolled in the study. The study could not be taken into consideration in the benefit assessment due to its very low significance and the joint representation of results on its safety without considering the respective original study.

Mortality

No deaths occurred in Study 108.

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 as an absolute change after 4-and 8-week intervals of treatment. The absolute change in $FEV_1$% compared to Weeks 4 and 8 amounted to an average of +6,4% in the TEZ/IVA arm and -0,3% in the control arm of Study 108. In Study 108, a statistically significant difference for the $FEV_1$% in favour of TEZ/IVA in comparison to placebo was determined (MD [95% CI]: 6.7 [5.5; 7.8]; $p < 0.0001$).

Different opinions on patient relevance to $FEV_1$% exist. The overall assessment on the extent of the additional benefit remains untouched by them.

*Pulmonary exacerbations, hospitalisation and i.v. antibiotics therapy due to 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 endpoints pulmonary exacerbations and hospitalisations due to pulmonary exacerbations, no statistically significant differences between TEZ/IVA and placebo were shown.

The endpoint i.v. antibiotics therapy due to 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 exacerbations. In addition, the endpoint does not supply any further information on the endpoint hospitalisations due to pulmonary exacerbations.

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

The endpoint symptoms was recorded using the hospital-specific CFQ-R (patient version) and comprised the domains respiratory system, weight problems as well as gastrointestinal. The CFQ-R is a questionnaire that measures the subjective perception through the patient's eye (so-called "patient-reported outcome, PRO"), i.e. his or her evaluation through the parents or guardian.

In the patient version for the domain respiratory system, a statistically significant benefit in favour of TEZ/IVA in comparison to placebo, an improvement by ≥ 4 points was determined in the responder assessment (RR [95% CI]): 1.9 [1.5; 2.4; $p < 0.0001$).

For the domain weight problems, a statistically significant difference in favour of TEZ/IVA compared to placebo (MD [95% CI] was shown: 3.6 [0.4; 6.7]; p=0.0265). For the gastrointestinal domain, a statistically significant difference to the disadvantage of TEZ/IVA compared to placebo (MD [95% CI] was shown: -2.6 [-4.8; -0.4]; p=0.0227). The 95% confidence interval of the Hedge's g does not lie fully outside of the irrelevant range of –0.2 to 0.2 so that it is not possible to derive whether the effects observed in the mean value differences are clinically relevant.

*Body Mass Index (BMI) and BMI z-score*

The BMI serves to evaluate a patient's body weight in relation to his or her physique. The BMI z-score serves as a standardised measure to adjust the BMI according to the patient's age and gender. The BMI endpoint is seen as an important parameter in evaluating development disorders in paediatric patients with cystic fibrosis.

For the endpoints absolute change in BMI and absolute change in BMI z-score, the results of Study 108 did not display any statistically significant differences between the TEZ/IVA arm and the control arm.

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 patient version of the CFQ-R, statistically significant and clinically relevant differences in favour of TEZ/IVA compared to placebo for the domain physical well-being (MD [95% CI] were determined in each case: 6.8 [4.0; 9.5]; p < 0.0001; Hedges' g [95%-CI]: 0.5 [0.3; 0.7]), vitality (MD [95% CI]: 7.9 [5.2; 10.5]; p < 0.0001; Hedges' g [95% CI]: 0.6 [0.3; 0.8]) as well as subjective perception of health (MD [95% CI]: 8.9 [6.7; 11.2]; p < 0.0001; Hedges' g [95% CI]: 0.7 [0.5; 1.0]).

For the domain emotional state (MD [95% CI]: 2.5 [0.8; 4.2]; p=0.0036), self-perception (MD [95% CI]: 2.2 [0.5; 3.9]; p=0.0123), burden of therapy (MD [95% CI]: 2.9 [0.9; 4.9]; p=0.0056), role functions (MD [95% CI]: 3.1 [0.8; 5.5]; p=0.0086) and social limitations (MD [95% CI]: 2.8 [1.0; 4.6]; p=0.0021), statistically significant differences in favour of TEZ/IVA compared to placebo. The 95% confidence interval of the Hedge's g does not lie fully outside of the irrelevant range of –0.2 to 0.2 so that it is not possible to derive whether the effects observed in the mean value differences are clinically relevant.

For the domain eating disorders, no statistically significant differences between the treatment groups were determined.

*Health-related quality of life measured through SF-12*

The SF-12 questionnaire consists of a physical domain (PCS) and a mental domain (MCS) whereby higher sum values characterise a better health condition.

For the domain PCS, a statistically significant, clinically relevant benefit for TEZ/IVA compared to placebo (MD [95% CI] was shown: 2.4 [1.5; 3.3]; p < 0.0001; Hedges' g [95% CI]: 0.5 [0.3; 0.7).] For the domain MCS, a statistically significant benefit for TEZ/IVA compared to placebo (MD [95% CI] was also shown: 1.3 [0.3; 2.4]; p=0.0113). The 95% confidence interval of the Hedges g in this case does not lie fully outside of the irrelevant range of –0.2 to 0.2 so that it is not possible to derive whether this effect is clinically relevant.

Side effects

In Study 108, for the endpoints serious adverse events (SAE) and adverse events (AE ≥ Grade 3) no statistically significant differences were shown in each case between the TEZ/IVA arm and the control arm.

For the endpoint withdrawal due to AEs, no statistically significant difference between TEZ/IVA and placebo was shown.

The most frequent adverse events at the SOC and PT level ( with a cut-off at ≥ 10% incidence in one of the study arms) in Study 108 were: Respiratory, thoracic and mediastinal disorders (SOC), especially coughing (PT), Infections and parasitic diseases (SOC), especially infectious pulmonary exacerbations of the CF (PT), gastrointestinal disorders (SOC), nervous system disorders (SOC), especially headaches (PT), as well as general disorders and administration site conditions (SOC) and investigations (SOC). In the Study, there was only one statistically significant difference for the endpoint respiratory, thoracic and mediastinal disorders (SOC) in favour of TEZ/IVA compared to the control group (RR [95% CI]: 0.8 [0.6; 0.997]; 0.0471).

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

Overall assessment/conclusion

For the benefit assessment of TEZ/IVA establishing treatment of cystic fibrosis (CF, mucoviscidosis) in patients 12 years of age and older who are heterozygous for the *F508del* mutation in the CFTR gene and display an RF mutation the CFTR gene, the multi-centre, randomised, double-blind, placebo-controlled cross-over phase III Study 108 was submitted. The results on mortality, morbidity, quality of life as well as side effects were yielded from Study 108.

No deaths occurred in Study 108.

Endpoints for the morbidity category were recorded as the percentage of forced expiratory volume per second ($FEV_1$ %); the symptoms were measured using CFQ-R, pulmonary exacerbations, hospitalisation and the i.v. antibiotics therapy due to pulmonary exacerbations, the BMI and the BMI z score.

For the endpoint symptoms recorded through the CFQ-R, a statistically significant and clinically relevant difference in favour of TEZ/IVA compared to the control group was shown in the domain respiratory system. For the domain weight problems, a statistically significant difference in favour of TEZ/IVA compared to placebo was shown, whereas for the gastrointestinal domain, a clinically significant difference to the disadvantage of TEZ/IVA compared to placebo was evident. The clinical relevance, however, of the changes shown remains unclear.

For the endpoints pulmonary exacerbations, hospitalisation due to pulmonary exacerbations as well as BMI and BMI z-score, no statistically significant differences between TEZ/IVA compared to placebo were shown.

In the category health-related quality of life, the endpoints CFQ-R and data SF-12 were recorded in Study 108. For the domains CFQ-R, physical well-being, vitality and subjective perception of health, a statistically significant and clinically relevant difference in favour of TEZ/IVA compared to placebo was determined in each case. For the domains emotional state, self-perception, burden of therapy, role function and social limitations in the CFR-Q, statistically significant differences in favour of TEZ/IVA compared to placebo were shown, whereby the clinical relevance of each of these statistically significant improvements cannot be assessed.

For the endpoint SF-12, the domain PCS showed a statistically significant benefit for TEZ/IVA compared to placebo that is additionally clinically relevant. For the domain MCS, a statistically significant benefit for TEZ/IVA compared to placebo was also shown, whose clinical relevance, however, cannot be assessed.

In the category side effects, there were no statistically significant benefits nor disadvantages determined in the treatment with TEZ/IVA compared to placebo.

Based on the chronic course of cystic fibrosis and the necessary long-term treatment of patients, the 8-week treatment period of the submitted RCT is viewed as insufficient in evaluating the sustainability of the effects. It remains unclear whether the displayed statistically significant benefits of TEZ/IVA compared to placebo in the category morbidity (symptoms through CFQ R) and quality of life (CFQ-R, SF-12) display long-term effects.

The indicated benefits can thus only be classified as no more than minor effects due to the short study period.

Based on the criteria in Section 5, Paragraph 7 of the German Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA arrived at the following conclusion taking the disease's degree of severity, the written statements and the oral hearing for patients 12 years of age and older with cystic fibrosis and who were heterozygous for the *F508del* mutation and showed one of the following mutations in the 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: minor additional benefit for treatment with TEZ/IVA.

### 2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Symkevi® with the active ingredient combination TEZ/IVA. TEZ/IVA is used in combination with ivacaftor 150 mg tablets establishing treatment of cystic fibrosis (CF) in patients 12 years of age and older who display homozygous for the F508del mutation or heterozygous for the F508del mutation and one of the following mutations in the 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.

In the therapeutic indications under review, there were two patient groups with cystic fibrosis a) patients 12 years of age and older who display homozygous for the *F508del* mutation and b) patients 12 years of age and older who display heterozygous for the *F508del* mutation and one of the following mutations in the 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.

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

For these two patient populations, the pharmaceutical manufacturer submitted the Phase III VX14-661-106 Study 106, a multi-centre, randomised, double-blind, placebo-controlled parallel group study justifying the marketing authorisation (TEZ/IVA vs. placebo; 24 weeks).

Furthermore, the pharmaceutical manufacturer also submitted the supporting Extension Study VX14-661-110, which, due to its very low relevance and the joint representation of safety results, could not be taken into consideration without taking the respective original study into account for the benefit assessment. In addition, the pharmaceutical manufacturer had submitted an indirect comparison between TEZ/IVA and LUM/IVA. Based on the prevalence of fundamentally higher value evidence (RCT) and in consideration of procedural provisions in the case of the benefit assessments of orphan drugs, the indirect comparison to LUM/IVA was not considered in the benefit assessment.

Study 106 resulted in a statistically significant difference in favour of TEZ/IVA compared to the control group for the endpoint pulmonary exacerbations in the category morbidity. In the domain respiratory system of the CFQ-R, a statistically significant and clinically relevant benefit for TEZ/IVA compared to the control group was shown.

For the endpoints hospitalisations due to pulmonary exacerbations as well as BMI and BMI z-score, no statistically significant differences between the treatment arms were determined.

In the category health-related quality of life, the endpoints CFQ-R and data SF-12 were recorded in Study 106. For the endpoint CFQ-R, the domains physical well-being, vitality, subjective perception of health burden of therapy and social limitations in each case showed statistically significant differences in favour of TEZ/IVA compared to placebo, whereby the clinical relevance of each of these statistically significant improvements cannot be assessed.

For the endpoint SF-12, the domain PCS showed a statistically significant benefit for TEZ/IVA compared to placebo, whereby the clinical relevance of this statistically significant improvement cannot be assessed. For the domain MCS, no statistically significant difference between the treatment groups could be determined.

In the category side effects, there were no statistically significant differences determined between the treatment arms TEZ/IVA and placebo.

Based on the criteria in Section 5 Paragraph 7 of the AM-NutzenV, the G-BA arrived at the following result taking the disease's degree of severity, the written statements and the oral

hearing for patients 12 years and older with cystic fibrosis and who were homozygous for the *F508del* mutation and determined a considerable additional benefit for the treatment with TEZ/IVA.

b) Patients 12 years of age and older with cystic fibrosis, who are heterozygous for the *F508del* mutation and who display one of the following mutations in the 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.

For this patient population, the pharmaceutical manufacturer submitted the multi-centre, randomised, double-blind, placebo-controlled cross-over phase III Study 108 to justify the marketing authorisation (TEZ/IVA vs. placebo; 8 weeks).

Furthermore, the pharmaceutical manufacturer also submitted the supporting Extension Study VX14-661-110, which, due to its very low relevance and the joint representation of safety results benefit assessment could not be taken into consideration without taking the respective original study into account for the benefit assessment.

For the endpoint symptoms recorded through the CFQ-R, a statistically significant and clinically relevant difference in favour of TEZ/IVA compared to the control group was shown in the domain respiratory system. For the domain weight problems, a statistically significant difference in favour of TEZ/IVA compared to placebo was displayed, whereas for the gastrointestinal domain, a clinically significant difference to the disadvantage of TEZ/IVA compared to placebo was evident. The clinical relevance, however, of the displayed changes remains unclear.

For the endpoints pulmonary exacerbations, hospitalisation due to pulmonary exacerbations as well as BMI and BMI z-score, no statistically significant differences between TEZ/IVA compared to placebo were shown.

In the category health-related quality of life, the endpoints CFQ-R and data SF-12 were recorded in Study 108. For the domains CFQ-R, physical well-being, vitality and subjective perception of health, a statistically significant and clinically relevant difference in favour of TEZ/IVA compared to placebo was determined in each case. For the domains emotional state, body image, burden of therapy, role function and social constraints in the CFR-Q, statistically significant differences in favour of TEZ/IVA compared to placebo were shown, whereby the clinical relevance of each of these statistically significant improvements cannot be assessed.

For the endpoint SF-12, the domain PCS showed a statistically significant benefit for TEZ/IVA compared to placebo, which is additionally clinically relevant. For the domain MCS, a statistically significant benefit for TEZ/IVA compared to placebo was also shown, whose clinical relevance, however, cannot be assessed.

In the category side effects, there were no statistically significant benefits nor disadvantages determined in the treatment with TEZ/IVA compared to placebo.

Based on the chronic course of cystic fibrosis and the necessary long-term treatment of patients, the 8-week treatment period of the submitted RCT is viewed as insufficient in evaluating the sustainability of the effects. It remains unclear whether the displayed statistically significant benefits of TEZ/IVA compared to placebo in the category Morbidity (symptoms through CFQ R) and quality of life (CFQ-R, SF-12) display long-term effects.

The indicated benefits can thus only be classified as no more than minor effects due to the short study period.

Based on the criteria in Section 5 Paragraph 7 of the German Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA arrived at the following conclusion taking the disease's degree of severity, the written statements and the oral hearing for

patients 12 years of age and older with cystic fibrosis and who were heterozygous for the *F508del* mutation and showed one of the following mutations in the 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, for the treatment with TEZ/IVA, minor additional benefit were determined.

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

In order to guarantee a consistent evaluation of the patient numbers taking the most recent resolution on the benefit assessment of medicinal products with new active ingredients (2 August 2018) based on Section 35a SGB V into consideration with the therapeutic indication "cystic fibrosis (CF, mucoviscidosis) in patients 6 years of age and older, who are homozygous for the *F508del* mutation in the CFTR gene", the G-BA applied the following derivation on the patient numbers:

The information on the number of patients concerns the target population in statutory health insurance (SHI).

It is assumed that there is an entire patient group of currently approx. 8,000 patients with cystic fibrosis in Germany[2].

This amount differs from the calculation in the dossier by the pharmaceutical manufacturer, who assumes that there are 5,720 patients with cystic fibrosis in the entire patient group. This piece of information, however, is subject to uncertainties and tends to represent an underestimate, since those patients without process data and without a current signed consent form were not been taken into account there. Furthermore, there currently are no indications that the number of patients in the entire patient group has changed significantly since the 2012 Annual Report (8,042 patients were ever reported and were still alive at the time. This number has already been adjusted to eliminate multiple responses in accordance with the information in the documentation).

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

1. The percentage of patients with confirmed homozygous *F508del* mutation in the CFTR gene is 46.89 %[3] (3,752 patients).
2. The percentage of patients 12 years of age and older in the entire patient group is approx. 72.6% [3] (2,724 patients).
3. Taking into account an 87.29% percentage of patients in statutory health insurance (SHI), there are 2,377 patients in the target population.

b) Patients from 12 years of age and older with cystic fibrosis, who are heterozygous for the *F508del* mutation and who display one of the following mutations in the 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.

1. Of the 10,855 alleles with known mutations, 7,569 alleles (69.73%) have a *F508del*

[2] https://www.muko.info/ (https://www.muko.info/englisch-version/) Website Mukoviszidose e.V. (German Cystic Fibrosis Association) [accessed 04.04.2019]
[3] Nährlich L, Burkhart M, Wiese B (Ed). German Cystic Fibrosis Registry: Annual Report 2016. Bonn: Cystic Fibrosis Institute (Mukoviszidose Institut); 2017. https://www.muko.info/fileadmin/user_upload/angebote/qualitaetsmanagement/register/berichtsband_2016.pdf.

mutation and 201 alleles (1.85 %) are either 2789+5G→A or 3849+10kbC→T[4]. Since 1.85% corresponds exclusively to 2 of the 14 mutations in the CFTR gene in this indication, this number is projected for the 14 mutations to be taken into account. For this purpose, information from a French and an American registry is taken into consideration. The percentage of 2,789+5G→A and 3,849+10kbC→T of all 14 mutations corresponds to approx. 59% in the American registry[5] and to approx. 50% in the French registry[6]. Based on this information, the result is 350 (= 8,000 * 69.73 % *1.85 % / 59 % * 2) to 413 (= 8,000 * 69.73 % * 1.85 % / 50 % * 2) patients.

2. The percentage of patients 12 years and older in the entire patient group is approx. 72.6% [3] (254 - 300 patients).
3. Taking into account an 87.29% share of patients covered by statutory health insurance (SHI), the result is 222 - 262 patients in the target population.

The range from 2,789+5G→A to 3,849+10kbC→T on all 14 mutations applied by the pharmaceutical manufacturer represents an overestimate.

### 2.3 Requirements for a quality-assured treatment

The requirements in the product information shall be taken into account. The European regulatory authority, European Medicines Agency (EMA) provides the contents of the product information for Symkevi® (active ingredient: Tezacaftor/ivacaftor) freely accessible at the following link (last access: 24. April 2019):

https://www.ema.europa.eu/en/documents/product-information/symkevi-epar-product-information_en.pdf (https://www.ema.europa.eu/documents/product-information/symkevi-epar-product-information_de.pdf)

The introduction and monitoring of treatment with Tezacaftor/ivacaftor may only be implemented in therapy with patients with cystic fibrosis by experienced physicians.

### 2.4 Treatment costs

The treatment costs are based on the details in the product information and the details in the Lauer-Taxe (status: 15. April 2019):

For the calculation of medicinal product costs, the number of packages required based on potency was initially used. Based on the determined number of packages required, the medicinal product costs were then calculated based on the costs per package after deducting the statutory discounts. The medicinal product costs were levied approximately both based on the pharmacy retail price level as well as after deducting the statutory discounts in accordance with Section 130a SGB V (Paragraph 1, 1a, 3a) and Section 130, Paragraph 1 SGB V for the sake of better comparability.

Treatment period:

[4] Nährlich L, Burkhart M, Wiese B (Ed). German Cystic Fibrosis Registry: Annual Report 2016. Bonn: Cystic Fibrosis Institute (Mukoviszidose Institut); 2017. https://www.muko.info/fileadmin/user_upload/angebote/qualitaetsmanagement/register/annual_report_2016.pdf (https://www.muko.info/fileadmin/user_upload/angebote/qualitaetsmanagement/register/berichtsband_2016.pdf).

[5] French Cystic Fibrosis Registry. Annual Data Report 2015, 05.2017.

[6] Cystic Fibrosis Foundation Patient Registry. 2016 Annual Data Report, 08.2017

| 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 | continuous, once a day | 365 | 1 | 365 |
| Ivacaftor | continuous, once a day | 365 | 1 | 365 |

Usage and consumption:

| Designation of the therapy | Dosage | Dose/patient/treatment days | Consumption according to potency /treatment day | Treatment days/ Patient/ year | Annual average consumption according to potency |
|---|---|---|---|---|---|
| Medicinal product to be assessed | | | | | |
| Tezacaftor/ivacaftor | 100 mg/ 150 mg | 100 mg/ 150 mg | 1 x 100 mg/150 mg | 365 | 365 x 100 mg/150 mg |
| Ivacaftor | 150 mg | 150 mg | 1 × 150 mg | 365 | 365 × 150 mg |

Costs:

**Costs of the medicinal product:**

| Designation of the therapy | Package size | Costs (pharmacy wholesale price) | Discount according to Section 130 SGB V | Discount according to Section 130a SGB V | Costs after deduction of statutory discounts |
|---|---|---|---|---|---|
| Medicinal product to be assessed | | | | | |
| Tezacaftor/ivacaftor | 28 FT | € 6,741,40 | € 1.77 | € 384.42 | € 6,355.21 |
| Ivacaftor | 56 FT | € 21,337.31 | € 1.77 | € 1,218.00 | € 20,117.54 |
| Abbreviations: FT = film tablets | | | | | |

Status Lauer-Taxe:15. April 2019

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 medical treatment or the prescription of other services when using the medicinal product to be assessed 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 the usual expenditure in the course of the treatment are not shown.

Since there are no regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed in accordance with the product information, no costs were incurred for additionally required SHI services had to be taken into consideration.

## 3. Bureaucratic costs

The proposed resolution does not create any new or amended information obligations for care providers in the sense of Appendix II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

## 4. Process sequence

On 5. November 2018, the pharmaceutical manufacturer submitted a dossier for the benefit assessment of Tezacaftor/ivacaftor to the G-BA in due time in accordance with Chapter 5, Section 8, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 1. März 2019 together with the IQWiG assessment of treatment costs and patient numbers on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 22. März 2019.

The oral hearing was held on 8. April 2019.

In a letter dated 09 April 2019, the G-BA was requested to initiate a supplementary assessment of the data presented in the hearing procedure. The amendment created by G-BA was transferred to the G-BA on 25 April 2019.

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. In addition, representatives of IQWiG also participate in the meetings.

The evaluation of the written statements received and the oral hearing were discussed at the subcommittee meeting on 7. Mai 2019, and the proposed resolution was approved.

At its meeting on 16. Mai 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

**Chronological course of the consultation**

| Meeting | Date | Subject of discussion |
|---|---|---|
| Subcommittee Medicinal products | 26. Februar 2019 | Knowledge of the benefit assessment by the G-BA |
| Working group Section 35a | 2. April 2019 | Information on written statements received; preparation of the oral hearing |
| Subcommittee Medicinal products | 8. April 2019 | Oral hearing carried out;<br>Request by the G-BA to assess the documents in addition |
| Working group Section 35a | 17. April 2019<br>30. April 2019 | Consultation on the dossier evaluation by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the statement procedure |
| Subcommittee Medicinal products | 7. Mai 2019 | Concluding discussion of the proposed resolution |
| Plenum | 16. Mai 2019 | Adoption of a resolution on the amendment of Appendix XII AM-RL |

Berlin, 16. May 2019

Federal Joint Committee
in accordance with Section 91 SGB V
Chair

Prof. Hecken