Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Ivacaftor/Tezacaftor/Elexacaftor (Exceeding the € 50 Million Limit, Cystic Fibrosis, Combination Treatment with Ivacaftor in Patients 12 Years and Older (Homozygous for F508del Mutation))

of 18 February 2021

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, the additional medical benefit is considered to be proven through the grant of the marketing authorisation in accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V. Evidence of the medical benefit and the additional medical 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 Chapter 5, Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT, exceeds € 50 million during the last 12 calendar months. In accordance with Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence in accordance with Chapter 5, Section 5, paragraphs 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5, Section 6 VerfO and prove the additional benefit compared with the appropriate comparator 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). 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 session 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 solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit provided is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by 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 to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product 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 of 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 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

Ivacaftor/tezacaftor/elexacaftor is approved as a medicinal product for the treatment of a rare disease in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs.

According to Section 35a, paragraph 1, sentence 11 SGB V, 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, evidence according to Section 35a, paragraph 1, sentence 3, Number 2 and 3 does not have to be submitted. This means that for these medicinal products, the dossier to be prepared by the pharmaceutical company does not have to contain any information on the medical benefit or the additional medical benefit in relation to the appropriate comparator therapy – as long as the privileged status applies by law. If the turnover of the orphan drug with the statutory health insurance at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT, exceeds an amount of € 50 million in the last 12 calendar months in a pending benefit assessment procedure according to Section 35a, paragraph 1 SGB V, the G-BA is entitled to request the pharmaceutical company to submit a dossier for the initiation of a benefit assessment procedure according to Section 35a, paragraph 1, sentence 11 SGB V in conjunction with Chapter 5 Section 12, No. 2 VerfO with complete evidence according to Section 35a, paragraph 1, sentence 3 SGB V. The procedural privilege of only limited depth of testing in the benefit assessment no longer applies. Procedural privilege is appropriate for medicinal products that have low turnover because of their marketing authorisation for rare diseases. If, however, the pharmaceutical company achieves a turnover of more than € 50 million with the medicinal product in the statutory health insurance in the last 12 calendar months, it is also reasonable to expect it to provide evidence of the additional benefit and to submit a complete dossier for this purpose, in particular for evidence of the medical benefit or the additional medical benefit in relation to the appropriate comparator therapy.

The G-BA carried out the benefit assessment and commissioned the IQWiG to assess the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 1 December 2020 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

On 22 January 2021, it was determined by the G-BA on the basis of information according to Section 84, paragraph 5, sentence 4 SGB V that the turnover of ivacaftor/tezacaftor/elexacaftor with the statutory health insurance at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT, exceeded € 50 million in the last 12 calendar months. The dossier submitted by the pharmaceutical company according to Section 35a, paragraph 1, sentence 11, 2nd half-sentence SGB V in conjunction with Chapter 5 Section 12 No. 1 VerfO without evidence of medical benefit in accordance with Section 35a, paragraph 1, sentence 3 No. 2 SGB V and without evidence of additional benefit in relation to the appropriate comparator therapy Section 35a, paragraph 1, sentence 3 No. 3 SGB V is not complete for the benefit assessment to be carried out by the G-BA after the abolition of the procedural facilitations because of exceeding the turnover threshold.

By letter dated 28 January 2021, the G-BA requested the pharmaceutical company in accordance with Section 35a, paragraph 1, sentence 12 SGB V to submit a complete dossier with the evidence according to Chapter 5, Section 5, paragraphs to 7 VerfO for the benefit assessment and to demonstrate the additional benefit compared with the appropriate comparator therapy in deviation from Section 35a, paragraph 1, sentence 11 SGB V. In the

letter of invitation, the pharmaceutical company was informed that because of the dossier submitted in the parallel procedure for the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient ivacaftor (new therapeutic indication: cystic fibrosis, combination therapy with ivacaftor/tezacaftor/elexacaftor in patients 12 years and older (homozygous for the F508del mutation)), it is possible to conduct a benefit assessment of the dossier submitted in the present procedure according to Section 35a, paragraph 1 sentence 11 SGB V with additional inclusion of the evidence according to Section 35a, paragraph 1, sentence 3 Nos. 2 and 3 SGB V from benefit assessment of the IQWiG from the aforementioned parallel procedure. It was also pointed out to the pharmaceutical company that the three-month deadline of Chapter 5, Section 12, No. 2 G-BA VerfO does not apply if it gives his consent to the inclusion of the evidence in accordance with Section 35a, paragraph 1, sentence 3, Nos. 2 and 3 SGB V from the benefit assessment of the iQWiG in the parallel proceedings because this deadline is primarily linked to the pharmaceutical company submitting a complete second dossier. With the written consent given by the pharmaceutical company on 28 January 2021 for the benefit assessment of the dossier according to Section 35a, paragraph 1, sentence 11 SGB V with additional inclusion of evidence in accordance with Section 35a, paragraph 1, sentence 3, Nos. 2 and 3 SGB V from the benefit assessment of the parallel proceedings, the submission of a second complete dossier has become obsolete.

In parallel to the present procedure on the active ingredient combination ivacaftor/tezacaftor/elexacaftor, the dossier assessment on ivacaftor in the corresponding therapeutic indication is being conducted by the IQWiG according to Section 35a, paragraph 1 SGB V. In accordance with the marketing authorisation, both medicinal products must be used in combination. The studies conducted always consider both proprietary medicinal products in free combination so that the underlying data basis is consistent and cannot be distinguished. Because all technical aspects in the procedures were discussed in the written statement procedure, a new opinion procedure in accordance with Chapter 5, Section 19 of the Rules of Procedure of the G-BA need not be conducted.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier assessment carried out by the G-BA (including the amendment), the assessment of treatment costs and patient numbers prepared by the IQWiG (IQWiG G20-18; Addendum G21-03), including the additional consideration of the benefit assessment of ivacaftor (A20-77; Addendum A21-03), and the written statements presented in the written and oral hearing procedure.

In 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

2.1.1 Approved therapeutic indication of ivacaftor/tezacaftor/elexacaftor (Kaftrio) in accordance with the product information

Kaftrio is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene or heterozygous for F508del in the CFTR gene with a minimal function (MF) mutation.

Therapeutic indication of the resolution (resolution of 18 February 2021):

Kaftrio is used as a combination regimen with ivacaftor 150 mg tablets for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Patients aged 12 years and older with cystic fibrosis (CF) who are homozygous for the F508del mutation in the CFTR gene

Appropriate comparator therapy for elexacaftor/tezacaftor/ivacaftor in combination with ivacaftor:

Lumacaftor/ivacaftor
or
Tezacaftor/ivacaftor in combination with ivacaftor

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 aged 12 years and older with cystic fibrosis who are homozygous for the F508del mutation”, CFTR modulators are approved in the following active ingredient combinations: Lumacaftor/ivacaftor (LUM/IVA) as well as tezacaftor/ivacaftor (TEZ/IVA) in combination with ivacaftor (IVA)

The following medicinal products are additionally approved for the symptomatic therapy of CF: Aztreonam, carbocisteine[1], ceftazidim, ciprofloxacin, colistimethate, dornase alfa, levofloxacin[2], 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.

[1] Approved for adolescents from the age of 13 years and adults with CF
[2] Approved only for adult patients with CF

On 3. For the patient group to be considered in the present therapeutic indication “patients aged 12 years and older with cystic fibrosis who are homozygous for the F508del mutation”, the following resolutions of the G-BA are available:

- For TEZ/IVA as a combination treatment with IVA, no additional benefit was identified for the patient group “patients aged 12 years and older” after re-assessment after exceeding the turnover limit of € 50 million (resolution of 17 December 2020).
- For IVA as a combination treatment with TEZ/IVA, 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:

- 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. For patients aged 12 years and older with CF who are homozygous for an F508del mutation, the active ingredients combinations LUM/IVA or TEZ/IVA + IVA approved for this mutation are equally eligible. Treatment with LUM/IVA or TEZ/IVA + IVA is therefore determined to be the 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 the symptomatic therapy of CF, in particular the antibiotic therapy of pulmonary infections (ceftazidine, colistimethate, tobramycin), the inhalation of medicinal products (mannitol, thornase alfa), enzyme substitution for pancreatic insufficiency (pancreatin), and the 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 of the additional benefit and significance of the evidence

In summary, the additional benefit of ivacaftor/tezacaftor/elexacaftor in combination with ivacaftor (IVA/TEZ/ELX + IVA) is assessed as follows:

<u>Patients aged 12 years and older with cystic fibrosis who are homozygous for the F508del mutation</u>

There is an indication of a major additional benefit.

Justification:

For the assessment of the additional benefit of IVA/TEZ/ELX + IVA in patients 12 years of age and older with cystic fibrosis who are homozygous for the F508del mutation in the CFTR gene, the 4-week Study VX17-445-103 (hereafter Study 103) compared with tezacaftor/ivacaftor in combination with ivacaftor (TEZ/IVA + IVA) was originally submitted.

In the written statement procedure, the pharmaceutical company submitted study VX18-445-109 (hereinafter referred to as Study 109) for the assessment of the additional benefit of IVA/TEZ/ELX + IVA in patients aged 12 years and older with cystic fibrosis who are homozygous for the F508del mutation in the CFTR gene. In the study, a comparison was made against the active comparator TEZ/IVA + IVA.

Overall, studies of 24 weeks are necessary for the benefit assessment in the therapeutic indication of cystic fibrosis. Because Study 109 is a 24-week study, the 4-week Study 103 is not used to derive the additional benefit.

Study 109 is a multi-centre, randomised, double-blind, parallel-group, controlled Phase III study. The total of 178 children, adolescents, and adults aged 12 years and older who were homozygous for the F508del mutation in the CFTR gene were randomised in a 1:1 ratio to the intervention arm (IVA/TEZ/ELX + IVA; N=88) or the comparator arm (TEZ/IVA + IVA; N = 88), stratified by FEV_1 (< 70% / ≥ 70%), age (< 18 / ≥ 18 years), and use of a CFTR modulator (yes/no). There had to be a confirmed diagnosis of cystic fibrosis, and an FEV1 of ≥ 40% and ≤ 90% of the normal value for age, sex, and height at the time of screening. Endpoints were surveyed in the categories of overall mortality, symptomatology, health-related quality of life, and adverse events (AEs). The study duration of Study 109 was 24 weeks.

Mortality

No deaths occurred in Study 109.

Morbidity

Pulmonary exacerbations and serious 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.

The endpoint pulmonary exacerbations was evaluated in two ways:

The endpoint pulmonary exacerbations was surveyed as a safety endpoint via the preferred term (PT) “infectious pulmonary exacerbation of cystic fibrosis”. The endpoint serious pulmonary exacerbations was also surveyed as a safety endpoint as a severe adverse event (SAE) via the PT “infectious pulmonary exacerbation of cystic fibrosis”.

This is a departure from previous procedures in which a pulmonary exacerbation was determined when at least four of 12 defined criteria (e.g. fever, increased dyspnoea, and haemoptysis) were met and new or modified antibiotic therapy was required. There are uncertainties as to whether the pulmonary exacerbations collected in accordance with PT would also have been assessed as pulmonary exacerbations according to the previously recognised operationalisation and whether a different patient population is thus addressed. Despite the resulting risk of bias, the patient relevance of the endpoint is not fundamentally questioned.

The endpoint serious pulmonary exacerbations was surveyed by means of SAE via the PT “infectious pulmonary exacerbation of cystic fibrosis”, which means that the bias in the recording of the morbidity endpoint can be regarded as low. The focus of this evaluation is on the serious events and is to be regarded as an approximation of the endpoint hospitalisation because of pulmonary exacerbations in the specific case.

The two evaluations show a different focus. Both are thus interpreted as relevant information for deriving an additional benefit.

Overall, both pulmonary exacerbations and serious pulmonary exacerbations show a statistically significant advantage of IVA/TEZ/ELX + IVA compared with TEZ/IVA + IVA.

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 of patients ("patient-reported outcome", PRO) and their assessment by parents/caregivers.

In accordance with the current procedure of IQWiG Methods 6.0[3], for patient-reported endpoints, the IQWiG considers a responder threshold for responder analysis of at least 15% of the scale range of an instrument (in the case of analyses conducted post hoc, exactly 15% of the scale range) to be necessary in order to reliably reflect a change that is noticeable for patients. Within the framework of the written statement procedure, the pharmaceutical company submitted responder analyses with a responder threshold of 15% of the scale range for all patient-reported endpoints.

For the domains respiratory system and weight problems, the responder analysis (improvement of at least 15 points) showed a statistically significant advantage of IVA/TEZ/ELX + IVA compared with TEZ/IVA + IVA.

For the domain gastrointestinal symptoms, the responder analysis (improvement of at least 15 points) showed no statistically significant difference between the treatment groups.

Body Mass Index (BMI) and BMI z-score

The BMI is used to assess body weight in relation to height. In the present indication, body weight or BMI is important because developmental disorders and disturbed nutrient uptake are among the typical signs of cystic fibrosis. This endpoint is considered to be a patient-relevant morbidity parameter, especially in children with characteristic, disease-related growth disorders. Data adjusted for age and sex (z-scores) are preferred over absolute values.

For the endpoint absolute change in BMI as well as the change in BMI z-score, a statistically significant difference in favour of IVA/TEZ/ELX + IVA compared with TEZ/IVA + IVA was found in Study 109. However, the relevance of this magnitude cannot be conclusively assessed because the patients included in both treatment groups already had a BMI in the normal range at baseline.

Forced one-second volume (FEV1%)

Forced one-second volume (FEV1), presented as the percentage of forced one-second volume relative to the standardised normal value as FEV1%, was measured as absolute change over 4 weeks and 24 weeks of treatment in Studies 103 and 109.

In Study 109, there was a statistically significant difference for FEV1% in favour of IVA/TEZ/ELX + IVA compared with TEZ/IVA + IVA.

There are different opinions on the patient relevance of FEV1%. The overall statement on the extent of the additional benefit remains unaffected.

[3] General Methods, Version 6.0. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), Cologne https://www.iqwig.de/de/methoden/methodenpapier.3020.html

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.

In Study 109, there was a statistically significant difference for sweat chloride concentration in favour of IVA/TEZ/ELX + IVA compared with TEZ/IVA + IVA.

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.

Quality of life

Health-related quality of life measured through CFQ-R

Quality of life was assessed by the validated, disease-specific quality of life instrument CFQ-R using the patient version and included the domains of physical well-being, emotional state, vitality, social limitations, role functioning, body image, eating disorders, burden of therapy, and subjective health assessment.

Here, too, within the framework of the written statement procedure, the pharmaceutical company submitted responder analyses with a responder threshold of 15% of the scale range for all patient-reported endpoints.

For the domains physical well-being, vitality, role functioning, burden of therapy, and subjective health assessment, a statistically significant advantage of IVA/TEZ/ELX + IVA compared with TEZ/IVA + IVA was shown for the responder analysis (improvement of at least 15 points).

For the domains emotional state, social limitations, body image, and eating disorders, there was no statistically significant difference between the treatment groups for the responder analysis (improvement by at least 15 points).

Side effects

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

For the endpoints SAEs and discontinuation because of AEs, there was no statistically significant difference between treatment groups.

In detail, the endpoint of the category specific AE “skin and subcutaneous tissue disorders” (SOC) showed a statistically significant disadvantage with an effect modification by the characteristic sex. For men, there is a statistically significant disadvantage for IVA/TEZ/ELX + IVA compared with TEZ/IVA + IVA. For women, there was no difference between the treatment groups. There are uncertainties regarding the clinical relevance of this sex-specific effect modification. This specific AE is therefore not considered further in the present assessment.

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

Overall assessment

For the benefit assessment of ivacaftor in combination with ivacaftor/tezacaftor/elexacaftor 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, Study 109 with a direct comparison

of IVA/TEZ/ELX + IVA and TEZ/IVA + IVA was used. Results on mortality, morbidity, quality of life, and side effects are available.

No deaths occurred in Study 109.

In the morbidity category, a direct comparison showed a statistically significant difference in favour of IVA/TEZ/ELX + IVA compared with TEZ/IVA + IVA for the endpoint pulmonary exacerbations and serious pulmonary exacerbations as well as for the domains of the symptomatology category of the CFQ-R (respiratory system and weight problems). For the domain gastrointestinal symptoms of the CFQ-R, there are no statistically significant difference between the treatment groups. The synopsis of the results on morbidity showed a difference relevant for the benefit assessment in favour of IVA/TEZ/ELX + IVA compared with TEZ/IVA + IVA.

In the health-related quality of life category, there was a statistically significant difference in favour of IVA/TEZ/ELX + IVA compared with TEZ/IVA + IVA for the domains of the health-related quality of life category of the CFQ-R (physical well-being, vitality, role functioning, burden of therapy, and subjective health assessment). For the domains emotional state, social limitations, body image, and eating disorders of the CFQ-R, there is no statistically significant difference between the treatment groups. The synopsis of the results on health-related quality of life showed a difference relevant for the benefit assessment in favour of IVA/TEZ/ELX + IVA compared with TEZ/IVA + IVA.

In the overall view, in the categories mortality and side effects, there were no statistically significant differences between IVA/TEZ/ELX + IVA compared with TEZ/IVA + IVA.

In summary, for patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene, the overall consideration of the results on mortality, morbidity, quality of life, and side effects show a major additional benefit for IVA/TEZ/ELX + IVA compared with TEZ/IVA + IVA.

Reliability of data (probability of additional benefit)

This assessment is based on the results of the RCT 109 on patients aged 12 years and older with cystic fibrosis who are homozygous for the F508del mutation in the CFTR gene.

Because the results of the present benefit assessment are based on only one study, at best indications of an additional benefit can be derived with regard to the reliability of data. The risk of bias of all included endpoints with appropriate operationalisation is rated as low. Overall, the reliability of data supporting the finding of an additional benefit must be classified in the “indication” category.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment for the active ingredient ivacaftor/tezacaftor/elexacaftor in combination with ivacaftor (IVA/TEZ/ELX + IVA). Ivacaftor/tezacaftor/elexacaftor (trade name: Kaftrio) was approved as an orphan drug, but has exceeded the € 50 million turnover limit.

The present resolution refers to the therapeutic indication “as a combination regimen with ivacaftor 150 mg tablets for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene”.

The G-BA determined lumacaftor/ivacaftor (LUM/IVA) or tezacaftor/ivacaftor in combination with ivacaftor (TEZ/IVA + IVA) as the appropriate comparator therapy.

For the assessment of the additional benefit, the pharmaceutical company presented a multi-centre, randomised, double-blind, placebo-controlled phase III study VX18-445-109 in which the administration of IVA/TEZ/ELX + IVA compared with TEZ/IVA + IVA was investigated in patients in the present therapeutic indication for a duration of 24 weeks.

In the overall view of the results of the study, there is a statistically significant difference in favour of IVA/TEZ/ELX + IVA in the endpoints pulmonary exacerbations and serious pulmonary exacerbations as well as in various domains of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) in the symptomatology category (respiratory system and weight problems) and the category health-related quality of life (physical well-being, vitality, role functioning, burden of therapy, and subjective health assessment).

There were no statistically significant differences between the treatment groups in the endpoints mortality and side effects as well as in the domains gastrointestinal symptoms, emotional state, social limitations, body image, and eating disorders of the CFQ-R.

In summary, for patients aged 12 years and older with cystic fibrosis who are homozygous for the F508del mutation in the CFTR gene, there is an indication of a major additional benefit of ivacaftor/tezacaftor/elexacaftor in combination with ivacaftor compared with tezacaftor/ivacaftor in combination with ivacaftor.

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

In order to ensure a consistent consideration of the patient numbers taking into account the most recent resolution (17 December 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 in patients aged 12 years and older who are homozygous for the F508del mutation, the G-BA uses the following derivation of the patient numbers:

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

A total patient group of currently approx. 8000 patients with cystic fibrosis in Germany is assumed[4].

This figure differs from the calculation in the dossier by the pharmaceutical company, which assumes a total population of 6340 patients with cystic fibrosis. However, this figure is subject to uncertainties and is underestimated because patients without event history and up-to-date consent forms were not taken into account. Furthermore, there is currently no indication that the number of patients in the overall collective has changed significantly since the 2012 report (8042 patients ever reported and still alive at that time). This number has already been adjusted to eliminate multiple responses in accordance with the information in the documentation).

1. The proportion of patients with confirmed homozygous F508del mutation in the CFTR gene is 46.4%[5] (3712 patients).
2. The proportion 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 2384 patients in the target population.

[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.

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 Kaftrio (active ingredient: Ivacaftor/tezacaftor/elexacaftor) at the following publicly accessible link (last access: 9 February 2021):

https://www.ema.europa.eu/en/documents/product-information/kaftrio-epar-product-information_de.pdf

Treatment with ivacaftor/tezacaftor/elexacaftor 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 February 2021).

For the cost representation, only the dosages of the general case are considered. If the treatment duration is unlimited, initial induction regimens are to be disregarded in the representation of costs. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

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.

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
Medicinal product to be assessed				
Ivacaftor/tezacaftor/elexacaftor	continuously, 1 × daily	365	1	365
Ivacaftor	continuously, 1 × daily	365	1	365
Appropriate comparator therapy				
Tezacaftor/ivacaftor	continuously, 1 × daily	365	1	365
Ivacaftor	continuously, 1 × daily	365	1	365
Lumacaftor/ivacaftor	continuously, 2 × daily	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	Annual average consumption by potency
Medicinal product to be assessed					
Ivacaftor/tezacaftor/elexacaftor	150 mg/100 mg/200 mg	150 mg/100 mg/200 mg	2 × 75 mg/50 mg/100 mg	365	730 × 75 mg/50 mg/100 mg
Ivacaftor	150 mg	150 mg	1 × 150 mg	365	365 × 150 mg
Appropriate comparator therapy					
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
Lumacaftor/ivacaftor	400 mg/250 mg	800 mg/500 mg	4 × 200 mg/125 mg	365	1460 × 200 mg/125 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated based on the rebates according to Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined 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					
Ivacaftor/tezacaftor/elexacaftor	56 FCT	€ 12,867.29	€ 1.77	€ 734.27	€12,131.25
Ivacaftor	56 FCT	€ 16,432.12	€ 1.77	€ 937.86	€ 15,492.49
Appropriate comparator therapy					
Tezacaftor/ivacaftor	28 FCT	€ 6,404.90	€ 1.77	€ 365.20	€ 6,037.93
Ivacaftor	56 FCT	€ 16,432.12	€ 1.77	€ 937.86	€ 15,492.49
Lumacaftor/ivacaftor	112 FCT	€ 12,076.19	€ 1.77	€ 689.09	€ 11,385.33
Abbreviations: FCT = film-coated tablets					

Pharmaceutical selling price (LAUER-TAXE®) as last revised: 1 February 2021

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 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.

No additionally required SHI services are taken into account for the cost representation.

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 25 February 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 26 August 2020, the pharmaceutical company submitted a dossier for the benefit assessment of ivacaftor/tezacaftor/elexacaftor 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 December 2020 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 22 December 2020.

The oral hearing was held on 11 January 2021.

The addendum prepared by the IQWiG was submitted to the G-BA on 28 January 2021.

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 9 February 2021, and the proposed resolution was approved.

At its session on 18 February 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	25 February 2020	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	24 November 2020	Information of the benefit assessment of the G-BA
Working group Section 35a	6 January 2021	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	11 January 2021	Conduct of the oral hearing
Working group Section 35a	20 January 2021 3 February 2021	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee on Medicinal Products	9 February 2021	Concluding discussion of the draft resolution
Plenum	18 February 2021	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 18 February 2021

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

Prof. Hecken