Gemeinsamer Bundesausschuss

# Justification

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Ivacaftor/ tezacaftor/ elexacaftor (new therapeutic indication: cystic fibrosis, combination regimen with ivacaftor, ≥ 2 years, non-Class I mutation (no gating mutation and no F508del mutation))

of 16 October 2025

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## 1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assess the benefit of all reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical studies the pharmaceutical company have conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decide on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

## 2. Key points of the resolution

The combination of active ingredients ivacaftor/ tezacaftor/ elexacaftor (Kaftrio) was listed for the first time on 1 September 2020 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

Kaftrio is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999.

Within the previously approved therapeutic indications, the turnover of ivacaftor/ tezacaftor/ elexacaftor with the statutory health insurance at pharmacy sales prices, including value-added tax exceeded € 30 million; therefore, proof must be provided for ivacaftor/ tezacaftor/ elexacaftor in accordance with Section 5, paragraph 1 through 6 VerfO, and the additional benefit, compared with the appropriate comparator therapy must be demonstrated.

On 4 April 2025, ivacaftor/ tezacaftor/ elexacaftor received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334 from 12.12.2008, sentence 7).

On 2 May 2025, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the combination of active ingredients ivacaftor/ tezacaftor/ elexacaftor with the new therapeutic indication "Treatment of cystic fibrosis (CF) in patients aged 2 years and older who have at least one non-Class I mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene" in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 August 2025 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a decision on whether an additional benefit of ivacaftor/ tezacaftor/ elexacaftor compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA have evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods[1] was not used in the benefit assessment of ivacaftor/ tezacaftor/ elexacaftor.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

## 2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

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

Kaftrio granules are indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in paediatric patients aged 2 to less than 6 years who have at least one non-Class I mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

Kaftrio tablets are indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one non-Class I mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

**Therapeutic indication of the resolution (resolution of 16.10.2025):**

Ivacaftor/ tezacaftor/ elexacaftor is indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 2 years and older who have at least one non-Class I mutation, which is not an F508del mutation and not a gating mutation, in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

### 2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults, adolescents and children aged 2 years and older with cystic fibrosis who have at least one non-Class I mutation, which is not an F508del mutation and not a gating mutation, in the CFTR gene.

a) Adults with cystic fibrosis who have at least one non-Class I mutation, which is not an F508del mutation and not a gating mutation, in the CFTR gene.

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

   - Best supportive care

b) Children and adolescents aged ≥ 6 to < 18 years with cystic fibrosis who have at least one non-Class I mutation, which is not an F508del mutation and not a gating mutation, in the CFTR gene.

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

   - Best supportive care

c) Children and adolescents aged ≥ 2 to < 6 years with cystic fibrosis who have at least one non-Class I mutation, which is not an F508del mutation and not a gating mutation, in the CFTR gene.

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

   - Best supportive care

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA 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.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

<u>Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:</u>

On 1. For the therapeutic indication of cystic fibrosis, the single active ingredient ivacaftor as well as the combinations of active ingredients lumacaftor/ ivacaftor and tezacaftor/ ivacaftor, each in combination with ivacaftor, are approved in addition to the combination of active ingredients ivacaftor/ tezacaftor/ ivacaftor in combination with ivacaftor, depending on the type of mutation present.

In addition, the following active ingredients are approved for the symptomatic treatment of cystic fibrosis: Aztreonam, carbocisteine[2], ceftazidime, ciprofloxacin, colistimethate, dornase alfa, Meronem, pancreatin and tobramycin.

[2] currently off the market

On 2. For the treatment of cystic fibrosis, nutritional measures, support of the respiratory function and physiotherapy (in the sense of the Remedies Directive) are basically considered as non-medicinal treatment measures.

On 3. No resolutions of the G-BA are available for the patient population to be considered in the present therapeutic indication.

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present therapeutic indication.

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

According to the current state of medical knowledge, there is no specific standard therapy that enables causal treatment of the disease with the corresponding type of mutation in adults, adolescents and children aged 2 years and older with cystic fibrosis who do not have an F508del mutation and not a gating mutation in the CFTR gene. The above-mentioned medicinal and non-medicinal therapy options alone are available for symptomatic therapy of this patient population. These are recommended in the present evidence for symptomatic therapy of cystic fibrosis, especially antibiotic therapy of pulmonary infections (ceftazidime, colistimethate, tobramycin), inhaled medicinal products (dornase alfa), enzyme substitution for pancreatic insufficiency (pancreatin), nutritional therapy, support of respiratory function and physiotherapy.

Against this background, best supportive care (BSC) is therefore determined as the appropriate comparator therapy for adults, adolescents and children aged 2 years and older with cystic fibrosis, who do not have an F508del mutation and not a gating mutation in the CFTR gene. BSC is defined as the therapy that ensures the best possible, patient-individual optimised, supportive treatment to alleviate symptoms and improve the quality of life (in particular antibiotics for pulmonary infections, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy (as defined in the Remedies Directive), making full use of all possible dietary measures).

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

### 2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor is assessed as follows:

<u>Adults, adolescents and children aged 2 years and older with cystic fibrosis who have at least one non-Class I mutation, which is not an F508del mutation and not a gating mutation, in the CFTR gene.</u>

a) Adults with cystic fibrosis who have at least one non-Class I mutation, which is not an F508del mutation and not a gating mutation, in the CFTR gene.

Hint for a major additional benefit.

b) Children and adolescents aged ≥ 6 to < 18 years with cystic fibrosis who have at least one non-Class I mutation, which is not an F508del mutation and not a gating mutation, in the CFTR gene.

Hint for a considerable additional benefit.

c) Children aged ≥ 2 to < 6 years with cystic fibrosis who have at least one non-Class I mutation, which is not an F508del mutation and not a gating mutation, in the CFTR gene.

Hint for a non-quantifiable additional benefit.

Justification:

For the benefit assessment, the pharmaceutical company submitted the results of the VX21-445-124 study. The study is a randomised, double-blind, placebo-controlled phase 3 study comparing ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor + BSC versus placebo + BSC.

307 patients aged 6 years and older with cystic fibrosis who had at least one mutation on the CFTR gene responsive to ivacaftor/ tezacaftor/ elexacaftor were enrolled in the study. In addition, patients had to have at least 1 of 18 qualifying mutations, with none of the two alleles allowed to have an F508del or gating mutation.

Randomisation was carried out in a 2:1 ratio into the treatment arms. The treatment duration was 24 weeks. Stratification was based on age (< 18 years vs ≥ 18 years), lung function ($FEV_1$ <70% vs ≥70% of the standardised normal value) and the CFTR mutation group (no residual function-like mutation vs ≥ 1 residual function-like mutation).

The change in lung function compared to the baseline value after 24 weeks was collected as the primary endpoint. Other patient-relevant endpoints included mortality, morbidity, health-related quality of life as well as side effects.

Extent and probability of the additional benefit

Mortality

Only one death occurred in the intervention arm of the VX21-445-124 study. For the endpoint of overall survival, there was therefore no statistically significant difference between the treatment groups.

Morbidity

*Pulmonary exacerbations*

Pulmonary exacerbations were defined as the simultaneous occurrence of at least four specific symptoms or clinical signs that made new or modified antibiotic therapy necessary. The evaluation was based on the percentage of those affected and the event rate per year in order to map both occurrence and frequency over the course of the study.

For the endpoint of pulmonary exacerbations, there was a statistically significant difference to the advantage of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor + BSC compared to placebo + BSC.

*Severe pulmonary exacerbations*

Hospitalisation due to pulmonary exacerbations was used as a measure of severe pulmonary exacerbations. The percentage of patients with at least one event was evaluated. Exacerbations that required intravenous antibiotic therapy are included in this endpoint and were not considered separately.

For the endpoint of severe pulmonary exacerbations, there was a statistically significant difference to the advantage of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor + BSC compared to placebo + BSC.

*Symptomatology (CFQ-R)*

The age-differentiated Cystic Fibrosis Questionnaire Revised (CFQ-R) instrument was used in the study for the assessment of symptomatology. The instrument comprises several versions: a patient version for different age groups (6 to 11 years, 12 to 13 years and ≥ 14 years) and a parent/ caregiver version (6 to 13 years). The patient version of the questionnaire was used for the assessment of the additional benefit. The parent/ caregiver version is presented additionally.

*Symptomatology (CFQ-R) – Respiratory system*

For the respiratory system domain of the CFQ-R, there was a statistically significant difference to the advantage of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor + BSC compared to placebo + BSC.

*Symptomatology (CFQ-R) – Gastrointestinal symptoms and weight problems*

For the domain of gastrointestinal symptoms and weight problems of the CFQ-R, there was no statistically significant difference between the treatment groups in each case.

*Sweat chloride concentration*

The determination of the sweat chloride concentration is used as standard in the diagnostic process as the values reflect the functionality of the CFTR protein, which is the pathophysiological cause of the disease. The endpoint is not considered directly patient-relevant and is considered additionally as the extent of a reduction in sweat chloride concentration is not directly associated with the extent of change in symptomatology.

*Body mass index (absolute change, z-score)*

The BMI is fundamentally relevant in this therapeutic indication as a measure of nutritional and developmental status. However, the mean BMI values were consistently within the normal age range in the VX21-445-124 study.

*Lung function using forced expiratory volume in 1 second ($FEV_1$)*

The $FEV_1$ endpoint is a lung function parameter. It is not only the change in lung function parameters such as the $FEV_1$ value that is relevant for the benefit assessment, but in particular the associated symptoms felt by patients and the resulting restriction in health-related quality of life.

The $FEV_1$ presented as the percentage of forced one second volume to standardised normal value as $FEV_1$%, was measured as absolute change over 24 weeks of treatment in the studies. There are different opinions on the patient relevance of $FEV_1$%. The overall statement on the extent of the additional benefit remains unaffected.

Quality of life

The age-differentiated Cystic Fibrosis Questionnaire Revised (CFQ-R) instrument was also used in the study for the assessment of the health-related quality of life. The instrument comprises several versions: a patient version for different age groups (6 to 11 years, 12 to 13 years and ≥ 14 years) and a parent/ caregiver version (6 to 13 years). The patient version of the questionnaire was used for the assessment of the additional benefit. The parent/ caregiver version is presented additionally.

*Health-related quality of life (CFQ-R) – Physical well-being, subjective health assessment*

For the domains of physical well-being and subjective health assessment (domain was only assessed in patients aged 14 years and older) of the CFQ-R, there was a statistically significant difference to the advantage of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor + BSC compared to placebo + BSC.

However, there are effect modifications for both domains due to the age and $FEV_1$ characteristics. For patients aged ≥ 18 years or with an $FEV_1$ < 70%, there were statistically significant differences in the relevant domains to the advantage of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor + BSC. However, for patients aged < 18 years or with an $FEV_1$ ≥ 70%, there was no statistically significant difference between the treatment arms.

It can be assumed that the age group < 18 years predominantly constituted subjects with an $FEV_1$ ≥ 70% as the patients aged 18 years and older enrolled in the VX21-445-124 study tended to have a lower $FEV_1$ at the start of the study. Against the background of the progressive course of cystic fibrosis, only the age characteristic is therefore taken into account in the following. The $FEV_1$ characteristic is not analysed separately.

*Health-related quality of life (CFQ-R) – Vitality, role functioning*

For the domains of vitality and role functioning (both domains were only assessed in patients aged 14 years and older) of the CFQ-R, there was a statistically significant difference to the advantage of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor + BSC compared to placebo + BSC.

*Health-related quality of life (CFQ-R) – Social limitations*

For the social limitation domain of the CFQ-R, there was a statistically significant difference to the advantage of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor + BSC compared to placebo + BSC. However, there was an effect modification due to the sex characteristic. For female patients, there was a statistically significant difference to the advantage of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor + BSC compared to placebo + BSC, but not for male patients. Since patients are equally affected by the disease

and a potential effect modification is only shown in a single domain of the CFQ-R, this characteristic is not further considered in the overall analysis.

*Health-related quality of life (CFQ-R) – Emotional state, body image, eating disorders, burden of therapy*

For the domains of emotional state, body image, eating disorders and burden of therapy of the CFQ-R, there was a statistically significant difference to the advantage of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor + BSC compared to placebo + BSC. However, the 95% confidence interval of the standardised mean difference is not completely outside the irrelevant range in each case, which is why a relevant difference cannot be derived.

Side effects

*SAEs, severe AEs and discontinuation due to AEs*

There was no statistically significant difference between the treatment groups for the endpoints of severe AEs and discontinuation due to AEs.

*Specific AEs*

For the endpoint "Rash (AEs)" in the category of non-serious/ non-severe side effects, there was a statistically significant difference to the disadvantage of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor + BSC compared to placebo + BSC.

Overall assessment

For patient population a)

In several endpoints for the adult patient population, there were statistically significant advantages for ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor + BSC compared to placebo + BSC.

There were no statistically significant differences in the endpoint category of mortality.

In the endpoint category of morbidity, there was a statistically significant advantage in favour of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor + BSC for both severe pulmonary exacerbations and pulmonary exacerbations overall. It should be noted that the endpoint "Pulmonary exacerbations" includes events that are already included in the endpoint "Severe pulmonary exacerbations", with the result that the endpoints are not completely independent. In addition, there was a statistically significant advantage in favour of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor + BSC in the respiratory system domain of the CFQ-R.

In the endpoint category of quality of life, there were statistically significant advantages of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor + BSC in each of the domains of physical well-being, vitality, social limitations, role functioning and subjective health assessment of the CFQ-R.

In the endpoint category of side effects, there were no statistically significant differences between the treatment groups for the endpoints of SAEs, severe AEs and discontinuation due to AEs respectively.

The overall assessment thus showed clear advantages for the adult patient population both in the endpoint category of morbidity and in health-related quality of life. Overall, a major additional benefit of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor compared with the appropriate comparator therapy of BSC was observed for adults with cystic

fibrosis who have at least one non-Class I mutation in the CFTR gene which is not an F508del mutation and not a gating mutation.

For patient population b)

In several endpoints for the patient population of children and adolescents aged ≥ 6 to < 18 years, there were statistically significant advantages for ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor + BSC compared to placebo + BSC.

There were no statistically significant differences in the endpoint category of mortality.

In the endpoint category of morbidity, there was a statistically significant advantage in favour of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor + BSC for both severe pulmonary exacerbations and pulmonary exacerbations overall. It should be noted that the endpoint "Pulmonary exacerbations" includes events that are already considered in the endpoint "Severe pulmonary exacerbations", with the result that the endpoints are not completely independent. In addition, there was a statistically significant advantage in favour of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor + BSC in the respiratory system domain of the CFQ-R.

In the endpoint category of quality of life, there were statistically significant advantages in favour of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor + BSC in the domains of vitality (≥ 14 years), social limitations and role functioning (≥ 14 years) of the CFQ-R. The vitality and role functioning domains were only assessed for patients aged 14 to 17 years. Whether these effects are also transferable to younger age groups remains unclear, as the corresponding domains of the CFQ-R were not intended for children under 14 years of age.

In the endpoint category of side effects, there were no statistically significant differences between the treatment groups for the endpoints of SAEs, severe AEs and discontinuation due to AEs respectively.

The overall assessment showed clear advantages for the patient population of children and adolescents aged ≥ 6 to < 18 years both in the endpoint category of morbidity and in health-related quality of life. When interpreting the results for children and adolescents aged ≥ 6 to < 18 years, it should be noted that patients in this age group have a lower symptom burden than adults due to the typically less advanced course of the disease. There is therefore uncertainty as to whether children and adolescents aged ≥ 6 to < 18 years benefit from the treatment to the same extent as adult patients in the short term. Long-term data are also not available.

Overall, a considerable additional benefit of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor compared with the appropriate comparator therapy of BSC was therefore observed for children and adolescents aged ≥ 6 to < 18 years with cystic fibrosis who have at least one non-Class I mutation in the CFTR gene which is not an F508del mutation and not a gating mutation.

Reliability of data (probability of additional benefit)

The present benefit assessment is based on the results of the randomised, double-blind, placebo-controlled phase 3 VX21-445-124 study.

The cross-endpoint risk of bias of the VX21-445-124 study is rated as low overall. However, there are uncertainties in the operationalisation of the endpoint "Severe adverse events". In addition, the transferability of the results to patients without the mutations investigated in the study is limited. Therefore, only indications of an additional benefit can be derived from the results of the study for both patient population a) and patient population b).

On patient population c)

Assessment with regard to transfer of additional benefit

Although no direct comparator study data are available for children aged ≥ 2 to < 6 years, the transferability of the results is based on the following aspects.

Firstly, cystic fibrosis is an inherited multisystem disease in which mutations in the CFTR gene cause disruptions in the chloride channel of exocrine glands. The pathophysiological background (disturbance in the chloride channel) of the patient population of ≥ 2 to < 6-year-old children relevant here is thus identical with that of older patients.

Cystic fibrosis is progressive, with younger children, such as the patient group considered here, showing fewer symptoms, without this fundamentally limiting the significance of patient-relevant endpoints. However, this means that an influence of the course of the disease on patient-relevant endpoints can only be measured to a limited extent.

The appropriate comparator therapy (BSC) determined by the G-BA is identical for all children, adolescents and adults with cystic fibrosis who have at least one non-Class I mutation in the CFTR gene which is not an F508del mutation and not a gating mutation. In this respect, a decisive criterion for transfer of evidence in the context of the early benefit assessment is given.

The standards to be applied for the acceptance of evidence-based on a low degree of evidence will also take into account the specificities and limitations of the conduct of paediatric clinical studies.

The assessment report of the European Medicines Agency (EMA)[3] also states that a transfer of the results from older patients to children aged ≥ 2 to < 6 years is considered appropriate. The marketing authorisation is based on comparable pharmacokinetic profiles and the common pathophysiological disease mechanism (CFTR dysfunction).

Overall, it is therefore assumed due to the identical genetic cause and comparable pathophysiology of the disease that the positive effects of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor from the VX21-445-124 study on 6 to 17-year-old children and adolescents are also transferable to children aged ≥ 2 to < 6 years.

In the case of transfer of evidence of the results from older patients, the overall assessment showed a non-quantifiable additional benefit of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor compared with the appropriate comparator therapy of BSC for children aged ≥ 2 to < 6 years with cystic fibrosis who have at least one non-Class I mutation in the CFTR gene which is not an F508del mutation and not a gating mutation.

Reliability of data (probability of additional benefit)

Due to the uncertainty caused by the transfer of the additional benefit to a younger patient population, a hint for reliability of data can only be identified.

[3] European Medicines Agency. Kaftrio/Kalydeco; Assessment report [online]. 2025 [accessed: 22.09.2025]. URL: https://www.ema.europa.eu/en/documents/variation-report/kaftrio-h-c-005269-ws-2551-epar-assessment-report-variation_en.pdf

### 2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the combination of active ingredients ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor.

The therapeutic indication assessed here is "Ivacaftor/ tezacaftor/ elexacaftor is indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 2 years and older who have at least one non-Class I mutation, which is not an F508del mutation and not a gating mutation, in the cystic fibrosis transmembrane conductance regulator (CFTR) gene".

Best Supportive Care (BSC) was determined as the appropriate comparator therapy.

In the therapeutic indication to be considered, the following patient populations were differentiated:

a) Adults with cystic fibrosis who have at least one non-Class I mutation, which is not an F508del mutation and not a gating mutation, in the CFTR gene.

b) Children and adolescents aged ≥ 6 to < 18 years with cystic fibrosis who have at least one non-Class I mutation, which is not an F508del mutation and not a gating mutation, in the CFTR gene.

c) Children and adolescents aged ≥ 2 to < 6 years with cystic fibrosis who have at least one non-Class I mutation, which is not an F508del mutation and not a gating mutation, in the CFTR gene.

For the benefit assessment, the pharmaceutical company submitted the results of the VX21-445-124 study. The study is a randomised, double-blind, placebo-controlled phase 3 study comparing ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor + BSC versus placebo + BSC. Patients aged 6 years and older with cystic fibrosis were enrolled in the study. Data for children aged ≥ 2 to < 6 years are not available.

On patient population a)

For the adult patient population, there were no statistically significant differences in the endpoint category of mortality.

In the endpoint category of morbidity, there was a statistically significant advantage in favour of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor + BSC for both severe pulmonary exacerbations and pulmonary exacerbations overall. In addition, there was a statistically significant advantage in favour of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor + BSC in the respiratory system domain of the CFQ-R.

In the endpoint category of quality of life, there were statistically significant advantages of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor + BSC in each of the domains of physical well-being, vitality, social limitations, role functioning and subjective health assessment of the CFQ-R.

In the endpoint category of side effects, there were no statistically significant differences between the treatment groups for the endpoints of SAEs, severe AEs and discontinuation due to AEs respectively.

The overall assessment thus showed clear advantages for the adult patient population both in the endpoint category of morbidity and in health-related quality of life.

Uncertainties arise with regard to the operationalisation of the endpoint "Severe adverse events". In addition, the transferability of the results to patients without the mutations investigated in the study is limited. The reliability of data is therefore classified in the "hint" category.

Overall, a hint for a major additional benefit of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor compared with the appropriate comparator therapy of BSC was therefore observed for adults with cystic fibrosis who have at least one non-Class I mutation in the CFTR gene which is not an F508del mutation and not a gating mutation.

On patient population b)

For children and adolescents aged ≥ 6 to < 18 years, there were no statistically significant differences in the endpoint category of mortality.

In the endpoint category of morbidity, there was a statistically significant advantage in favour of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor + BSC for both severe pulmonary exacerbations and pulmonary exacerbations overall. In addition, there was a statistically significant advantage in favour of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor + BSC in the respiratory system domain of the CFQ-R.

In the endpoint category of quality of life, there were statistically significant advantages in favour of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor + BSC in the domains of vitality, social limitations and role functioning of the CFQ-R. The vitality and role functioning domains were only assessed for patients aged 14 to 17 years. Whether these effects are also transferable to younger age groups remains unclear, as the corresponding domains of the CFQ-R are not intended for children under 14 years of age.

In the endpoint category of side effects, there were no statistically significant differences between the treatment groups for the endpoints of SAEs, severe AEs and discontinuation due to AEs respectively.

Uncertainties arise with regard to the operationalisation of the endpoint "Severe adverse events". In addition, the transferability of the results to patients without the mutations investigated in the study is limited. The reliability of data is therefore classified in the "hint" category.

The overall assessment showed clear advantages for children and adolescents aged ≥ 6 to < 18 years both in the endpoint category of morbidity and in health-related quality of life. However, it remains unclear whether children and adolescents aged ≥ 6 to < 18 years benefit from the treatment to the same extent as adult patients in the short term. Long-term data are also not available.

Overall, a hint for a considerable additional benefit of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor compared with the appropriate comparator therapy of BSC was therefore observed for children and adolescents aged ≥ 6 to < 18 years with cystic fibrosis who have at least one non-Class I mutation in the CFTR gene which is not an F508del mutation and not a gating mutation.

On patient population c)

No direct comparator study data are available for children aged ≥ 2 to < 6 years. Nevertheless, advantages can also be derived for this patient population by transfer of evidence of the results from older patients. The transferability of the results is based on the following aspects.

The underlying cause of the disease – a mutation in the CFTR gene – is the same for all age groups. As the disease is progressive, younger children usually show fewer symptoms, without this fundamentally limiting the significance of patient-relevant endpoints.

In addition, the appropriate comparator therapy of BSC determined by the G-BA is identical for all age groups. This represents a decisive criterion for transfer of evidence in the context of the early benefit assessment.

The assessment report of the European Medicines Agency (EMA) also states that a transfer of the results from older patients to children aged ≥ 2 to < 6 years is considered appropriate. The marketing authorisation is based on comparable pharmacokinetic profiles and the common pathophysiological disease mechanism (CFTR dysfunction).

By transfer of the results of the VX21-445-124 study from 6 to 17-year-old children and adolescents to children aged ≥ 2 to < 6 years with cystic fibrosis who have at least one non-Class I mutation in the CFTR gene which is not an F508del mutation and not a gating mutation, the overall assessment showed a hint for a non-quantifiable additional benefit of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor compared with the appropriate comparator therapy of BSC.

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

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

The information is based on patient numbers based on the information provided by the pharmaceutical company in the dossier.

The number of patients stated by the pharmaceutical company is an underestimate overall. The pharmaceutical company's calculation is based exclusively on the patient population of the mucoviscidosis (cystic fibrosis) registry with documented process data and current consent. However, taking into account all patients with cystic fibrosis in Germany, who are alive or have died in the reference period, would be significant.

No data on the age structure of the target population is available in the dossier.

An estimate based on the mucoviscidosis (cystic fibrosis) registry shows a percentage of 64.0% for adult patients (corresponding to around 240 patients), 26.7% for children and adolescents aged ≥ 6 to < 18 years (corresponding to around 100 patients) and 9.3% for children aged ≥ 2 to < 6 years (corresponding to around 35 patients).

This calculation does not take into account the group of patients with a mutation not defined in the product information.

## 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: 07 August 2025):

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

Treatment with ivacaftor/ tezacaftor/ elexacaftor should only be initiated and monitored by specialists experienced in treating 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: 15 August 2025). The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

For dosage depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population"[4] and "Microcensus 2021 – body measurements of the population"[5] were applied.

The average body weight of a 2-year-old child is 14.1 kg and that of a 5-year-old 20.8 kg. According to the product information, children weighing 14 kg or more receive 1 sachet of granules of 75 mg/ 50 mg/ 100 mg ivacaftor/ tezacaftor/ elexacaftor 1 x daily in the morning and 1 sachet of granules of ivacaftor 75 mg 1 x daily in the evening.

The dosage of ivacaftor/ tezacaftor/ elexacaftor recommended for children varies depending on body weight. The average body weight of 6-year-olds is 23.6 kg. According to the product information, children with a body weight of up to 30 kg receive 2 tablets of 37.5 mg/ 25 mg/ 50 mg ivacaftor/ tezacaftor/ elexacaftor 1 x daily and 1 tablet of 75 mg ivacaftor 1 x daily. Above a body weight of 30 kg (corresponding to an age of 9 years), the children receive 2 tablets of 75 mg/ 50 mg/ 100 mg ivacaftor/ tezacaftor/ elexacaftor 1 x daily and 1 tablet of 150 mg ivacaftor 1 x daily.

The treatment costs for best supportive care are different from patient to patient. Because best supportive care has been determined as an appropriate comparator therapy, this is also reflected in the medicinal product to be assessed. The type and scope of best supportive care can vary depending on the medicinal product to be assessed and the comparator therapy.

[4] Federal Health Reporting. Average body measurements of the population (2017, both sexes, 1 year and older), www.gbe-bund.de

[5] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

a) Adults with cystic fibrosis who have at least one non-Class I mutation, which is not an F508del mutation and not a gating mutation, in the CFTR gene.

Treatment period:

| 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 x daily | 365.0 | 1 | 365.0 |
| Ivacaftor | Continuously, 1 x daily | 365.0 | 1 | 365.0 |
| Best supportive care | Different from patient to patient | | | |
| Appropriate comparator therapy | | | | |
| Best supportive care | Different from patient to patient | | | |

Consumption:

| Designation of the therapy | Dosage/ application | Dose/ patient/ treatment days | Consumption by potency/ treatment day | Treatment days/ patient/ year | Average annual consumption by potency |
|---|---|---|---|---|---|
| Medicinal product to be assessed | | | | | |
| Ivacaftor/ tezacaftor/ elexacaftor | 150 mg/ 100 mg/ 200 mg | 150 mg/ 100 mg/ 200 mg | 2 x 75 mg/ 50 mg/ 100 mg | 365.0 | 730 x 75 mg/ 50 mg/ 100 mg |
| Ivacaftor | 150 mg | 150 mg | 1 x 150 mg | 365.0 | 365 x 150 mg |
| Best supportive care | Different from patient to patient | | | | |
| Appropriate comparator therapy | | | | | |
| Best supportive care | Different from patient to patient | | | | |

b) Children and adolescents aged ≥ 6 to < 18 years with cystic fibrosis who have at least one non-Class I mutation, which is not an F508del mutation and not a gating mutation, in the CFTR gene.

Treatment period:

| 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 x daily | 365.0 | 1 | 365.0 |
| Ivacaftor | Continuously, 1 x daily | 365.0 | 1 | 365.0 |
| Best supportive care | Different from patient to patient | | | |
| Appropriate comparator therapy | | | | |
| Best supportive care | Different from patient to patient | | | |

Consumption:

| Designation of the therapy | Dosage/ application | Dose/ patient/ treatment days | Consumption by potency/ treatment day | Treatment days/ patient/ year | Average annual consumption by potency |
|---|---|---|---|---|---|
| Medicinal product to be assessed | | | | | |
| Ivacaftor/ tezacaftor/ elexacaftor | 75 mg/ 50 mg/ 100 mg – 150 mg/ 100 mg/ 200 mg | 75 mg/ 50 mg/ 100 mg – 150 mg/ 100 mg/ 200 mg | 2 x 37.5 mg/ 25 mg/ 50 mg – 2 x 75 mg/ 50 mg/ 100 mg | 365.0 | 730 x 37.5 mg/ 25 mg/ 50 mg – 730 x 75 mg/ 50 mg/ 100 mg |
| Ivacaftor | 75 mg – 150 mg | 75 mg – 150 mg | 1 x 75 mg – 1 x 150 mg | 365.0 | 365 x 75 mg – 365 x 150 mg |
| Best supportive care | Different from patient to patient | | | | |
| Appropriate comparator therapy | | | | | |
| Best supportive care | Different from patient to patient | | | | |

c) Children and adolescents aged ≥ 2 to < 6 years with cystic fibrosis who have at least one non-Class I mutation, which is not an F508del mutation and not a gating mutation, in the CFTR gene.

Treatment period:

| 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 x daily | 365.0 | 1 | 365.0 |
| Ivacaftor | Continuously, 1 x daily | 365.0 | 1 | 365.0 |
| Best supportive care | Different from patient to patient | | | |
| Appropriate comparator therapy | | | | |
| Best supportive care | Different from patient to patient | | | |

Consumption:

| Designation of the therapy | Dosage/ application | Dose/ patient/ treatment days | Consumption by potency/ treatment day | Treatment days/ patient/ year | Average annual consumption by potency |
|---|---|---|---|---|---|
| Medicinal product to be assessed | | | | | |
| Ivacaftor/ tezacaftor/ elexacaftor | 75 mg/ 50 mg/ 100 mg | 75 mg/ 50 mg/ 100 mg | 1 x 75 mg/ 50 mg/ 100 mg | 365.0 | 365 x 75 mg/ 50 mg/ 100 mg |
| Ivacaftor | 75 mg | 75 mg | 1 x 75 mg | 365.0 | 365 x 75 mg |
| Best supportive care | Different from patient to patient | | | | |
| Appropriate comparator therapy | | | | | |
| Best supportive care | Different from patient to patient | | | | |

a) to c)

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of

the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

**Costs of the medicinal products:**

| Designation of the therapy | Packaging 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 75 mg/ tezacaftor 50 mg/ elexacaftor 100 mg | 28 GRA | € 10,132.01 | € 1.77 | € 578.05 | € 9,552.19 |
| Ivacaftor 37.5 mg/ tezacaftor 25 mg/ elexacaftor 50 mg | 56 FTA | € 10,132.01 | € 1.77 | € 578.05 | € 9,552.19 |
| Ivacaftor 75 mg/ tezacaftor 50 mg/ elexacaftor 100 mg | 56 FTA | € 10,132.01 | € 1.77 | € 578.05 | € 9,552.19 |
| Ivacaftor 75 mg | 56 GRA | € 11,707.62 | € 1.77 | € 668.03 | € 11,037.82 |
| Ivacaftor 75 mg | 28 FTA | € 5,859.02 | € 1.77 | € 334.01 | € 5,523.24 |
| Ivacaftor 150 mg | 56 FTA | € 11,707.62 | € 1.77 | € 668.03 | € 11,037.82 |
| Best supportive care | Different from patient to patient | | | | |
| Appropriate comparator therapy | | | | | |
| Best supportive care | Different from patient to patient | | | | |
| Abbreviations: FCT = film-coated tablets; GRA = granules | | | | | |

LAUER-TAXE® last revised: 15 August 2025

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

## 2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing

authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA have decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA have decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic

indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA have decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to

Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

a) Adults with cystic fibrosis who have at least one non-Class I mutation, which is not an F508del mutation and not a gating mutation, in the CFTR gene.

   – No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

b) Children and adolescents aged ≥ 6 to < 18 years with cystic fibrosis who have at least one non-Class I mutation, which is not an F508del mutation and not a gating mutation, in the CFTR gene.

   – No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

c) Children and adolescents aged ≥ 2 to < 6 years with cystic fibrosis who have at least one non-Class I mutation, which is not an F508del mutation and not a gating mutation, in the CFTR gene.

   – No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

   Product information for ivacaftor/ tezacaftor/ elexacaftor (Kaftrio) in combination with ivacaftor; Kaftrio 37.5 mg/ 25 mg/ 50 mg/ 75 mg/ 50 mg/ 100 mg film-coated tablets; last

revised: April 2025 & Kaftrio 60 mg/ 40 mg/ 80 mg/ 75 mg/ 50 mg/ 100 mg granules in sachet; last revised: April 2025

## 3. Bureaucratic costs calculation

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 their session on 2 April 2024, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 2 May 2025, 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, paragraph 1, number 2 sentence 2 VerfO.

By letter dated 2 May 2025, in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the combination of active ingredients ivacaftor/ tezacaftor/ elexacaftor.

The dossier assessment by the IQWiG was submitted to the G-BA on 30 July 2025, and the written statement procedure was initiated with publication on the G-BA website on 1 August 2025. The deadline for submitting statements was 22 August 2025.

The oral hearing was held on 8 September 2025.

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 was discussed at the session of the Subcommittee on 7 October 2025, and the proposed draft resolution was approved.

At their session on 16 October 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

**Chronological course of consultation**

| Session | Date | Subject of consultation |
|---|---|---|
| Subcommittee on Medicinal Products | 2 April 2024 | Determination of the appropriate comparator therapy |
| Working group Section 35a | 2 September 2025 | Information on written statements received; preparation of the oral hearing |
| Subcommittee on Medicinal Products | 8 September 2025 | Conduct of the oral hearing,<br>if applicable: commissioning of the IQWiG with the supplementary assessment of documents |
| Working group Section 35a | 16 September 2025<br>30 September 2025 | Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure |
| Subcommittee on Medicinal Products | 7 October 2025 | Concluding discussion of the draft resolution |
| Plenum | 16 October 2025 | Adoption of the resolution on the amendment of the Pharmaceuticals Directive |

Berlin, 16 October 2025

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken