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 (a gating mutation and not an F508del mutation))

of 16 October 2025

Contents

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.

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 a gating mutation and not an F508del 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.

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 a gating mutation and not an F508del mutation, in the CFTR gene

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

- Ivacaftor

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.

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

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.

On 2. In 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. Resolutions on the active ingredient ivacaftor from 20 February 2020 are available for the patient population to be considered in this 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.

The active ingredient ivacaftor as monotherapy is approved for adults, adolescents and children aged 2 years and older with cystic fibrosis who have a gating mutation but not an F508del mutation in the CFTR gene. The guidelines and the statements of the scientific-medical societies recommend causal therapy initiated early with a CFTR modulator. Against this background, the G-BA determined the active ingredient ivacaftor as the appropriate comparator therapy for these patients. Patients should also be offered symptomatic therapy, if indicated, with the above-mentioned medicinal symptomatic therapies as well as non-medicinal therapy options.

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] currently off the market

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:

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

Justification:

No direct comparator data of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor versus the appropriate comparator therapy of ivacaftor are available.

To supplement the evidence base, the pharmaceutical company conducted a search for further studies on the intervention and the appropriate comparator therapy. As part of this search, the pharmaceutical company identified the observational studies VX22-CFD-016, HEOR-23-445-014, Burgel 2024 and Cromwell 2024 as well as the single-arm extension study VX21-445-125 of the VX21-445-124 RCT. The pharmaceutical company did not identify any suitable studies for the appropriate comparator therapy.

The VX21-445-124 study primarily used by the pharmaceutical company is not suitable for deriving an additional benefit. The study is a randomised controlled trial comparing ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor versus placebo, each in addition to basic therapy. There was no comparison with the appropriate comparator therapy of ivacaftor determined by the G-BA.

The single-arm observational studies (VX22-CFD-016, HEOR-23-445-014, Burgel 2024, Cromwell 2024) and the extension study VX21-445-125 used by the pharmaceutical company for supplementation purposes also do not allow a comparison with the appropriate comparator therapy determined by the G-BA.

Thus, the data presented by the pharmaceutical company are not suitable to derive conclusions on the additional benefit of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor in comparison with the appropriate comparator therapy.

An additional benefit is therefore not proven.

2.1.4 Summary of the assessment

This assessment concerns the benefit assessment of the medicinal product Kaftrio with the active ingredients ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor for the treatment of adults, adolescents and children aged 2 years and older with cystic fibrosis who have at least one non-Class I mutation, which is a gating mutation and not an F508del mutation, in the CFTR gene.

The G-BA determined the appropriate comparator therapy to be a therapy with ivacaftor.

For the benefit assessment, the pharmaceutical company did not present any study results comparing ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor with the appropriate comparator therapy.

The VX21-445-124 study primarily used by the pharmaceutical company is a randomised controlled trial comparing ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor

versus placebo, each in addition to basic therapy. There was no comparison with the appropriate comparator therapy of ivacaftor determined by the G-BA.

Overall, the data presented are therefore not suitable to derive an additional benefit of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor over the appropriate comparator therapy in adults, adolescents and children aged 2 years and older with cystic fibrosis who have at least one non-Class I mutation, which is a gating mutation and not an F508del mutation, in the CFTR gene.

An additional benefit is therefore not proven.

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.

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: 06 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).

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"[3] and "Microcensus 2021 – body measurements of the population"[4] 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 once daily in the morning and 1 sachet of granules of ivacaftor 75 mg once daily in the evening.

The average body weight of a 6-year-old child is 23.6 kg and that of a 11-year-old adolescent 42.1 kg. The dosage of ivacaftor/ tezacaftor/ elexacaftor recommended for children varies depending on body weight. According to the product information, children up to a body weight of 30 kg receive 1 x daily 2 tablets of 37.5 mg/ 25 mg/50 mg ivacaftor/ tezacaftor/ elexacaftor and 1 x daily 1 tablet of 75 mg ivacaftor. Above a body weight of 30 kg, children receive 1 x daily 2 tablets of 75 mg/ 50 mg/ 100 mg ivacaftor/ tezacaftor/ elexacaftor and 1 x daily 1 tablet of 150 mg ivacaftor.

According to the product information, patients aged 12 years and over are given two 75 mg ivacaftor/ 50 mg tezacaftor/ 100 mg elexacaftor tablets 1 x daily in the morning and one 150 mg ivacaftor tablet in the evening.

For ivacaftor monotherapy, children with a body weight between 14 kg and 25 kg receive 2 x 75 mg ivacaftor granules daily. In the case of monotherapy, children with a body weight of 25 kg or more receive 2 x 150 mg ivacaftor in the form of film-coated tablets daily.

Adults, adolescents and children aged 2 years and older with cystic fibrosis who have one non-Class I mutation, which is a gating mutation and not an F508del 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
Appropriate comparator therapy				
Ivacaftor	Continuously, 2 x daily	365.0	1	365.0

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

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

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					
GRA	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
TAB	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[5] - 150 mg	75 mg - 150 mg	1 x 75 mg - 1 x 150 mg	365.0	365 x 75 mg - 365 x 150 mg
Appropriate comparator therapy					
Ivacaftor	75 mg[5] - 150 mg	75 mg - 150 mg	2 x 75 mg - 2 x 150 mg	365.0	730 x 75 mg - 730 x 150 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates 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.

[5] 75 mg - Dosage for the administration of granules or tablets

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
Appropriate comparator therapy					
Ivacaftor 75 mg	56 GRA	€ 11,707.62	€ 1.77	€ 668.03	€ 11,037.82
Ivacaftor 150 mg	56 FTA	€ 11,707.62	€ 1.77	€ 668.03	€ 11,037.82
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:

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

References:
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,
Working group Section 35a	16 September 2025 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