Ivacaftor/tezacaftor/elexacaftor (combination with ivacaftor; cystic fibrosis; ≥ 2 years, at least 1 non-Class I mutation, including gating mutation, excluding F508del mutation)

Benefit assessment according to §35a SGB V[1]

EXTRACT

Project: A25-62 Version: 1.0 Status: 30 Jul 2025 DOI: 10.60584/A25-62_en

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Ivacaftor/Tezacaftor/Elexacaftor (Kombination mit Ivacaftor; zystische Fibrose, ≥ 2 Jahre, mindestens 1 Nicht-Klasse-I-Mutation, inklusive Gating-Mutation, exklusive F508del-Mutation) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Ivacaftor/tezacaftor/elexacaftor (combination with ivacaftor; cystic fibrosis; ≥ 2 years, at least 1 non-Class I mutation, including gating mutation, excluding F508del mutation) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

2 May 2025

Internal Project No.

A25-62

DOI-URL

https://doi.org/10.60584/A25-62_en

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50679 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Recommended citation

Institute for Quality and Efficiency in Health Care. Ivacaftor/tezacaftor/elexacaftor (combination with ivacaftor; cystic fibrosis; ≥ 2 years, at least 1 non-Class I mutation, including gating mutation, excluding F508del mutation); Benefit assessment according to §35a SGB V; Extract [online]. 2025 [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/A25-62_en.

Keywords

Ivacaftor, Tezacaftor, Elexacaftor, Cystic Fibrosis, Child – Preschool, Child, Adolescent, Adult, Benefit Assessment

Medical and scientific advice

No advisor on medical and scientific questions was available for the present dossier assessment.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by one other person.

IQWiG thanks the respondent and the patient organization ‘Mukoviszidose e. V.’ for participating in the written exchange and for their support. The respondent and ‘Mukoviszidose e. V.’ were not involved in the actual preparation of the dossier assessment.

IQWiG employees involved in the dossier assessment

- Christian Siebel
- Charlotte Guddat
- Lisa Junge
- Stefan Kobza
- Ulrike Lampert
- Sabine Ostlender
- Daniela Preukschat
- Min Ripoll
- Yvonne Zens

Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CFTR	cystic fibrosis transmembrane conductance regulator gene
EMA	European Medicines Agency
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug ivacaftor/tezacaftor/elexacaftor (in combination with ivacaftor). The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the 'company'). The dossier was sent to IQWiG on 2 May 2025.

Research question

The aim of this report is to assess the added benefit of ivacaftor/tezacaftor/elexacaftor in combination with ivacaftor (hereinafter referred to as ivacaftor/tezacaftor/elexacaftor + ivacaftor) in comparison with ivacaftor as the appropriate comparator therapy (ACT) in patients with cystic fibrosis aged 2 years and older who have at least one non-Class I mutation, including at least one gating mutation and excluding an F508del mutation, in the cystic fibrosis transmembrane conductance regulator gene (CFTR).

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of ivacaftor/tezacaftor/elexacaftor + ivacaftor

Therapeutic indication	**ACT**[a]
Patients with cystic fibrosis aged 2 years and older who have at least one non-Class I mutation, including at least one gating mutation and excluding an F508del mutation, in the CFTR gene	ivacaftor
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee	

The company designated ivacaftor as the ACT, thus following the G-BA's specification.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Studies with a minimum duration of 24 weeks were used for the derivation of the added benefit.

Results

Evidence provided by the company

A review of the completeness of the study pool did not find any randomized controlled trials (RCTs) on the direct comparison of ivacaftor/tezacaftor/elexacaftor + ivacaftor versus the ACT ivacaftor in the therapeutic indication in question.

As the company did not identify any RCTs on the direct or adjusted indirect comparison of ivacaftor/tezacaftor/elexacaftor + ivacaftor versus the ACT, it conducted an additional information retrieval for further studies with the intervention and the ACT. In this information retrieval, the company identified the single-arm observational studies VX22-CFD-016, HEOR-23-445-014, Burgel 2024 and Cromwell 2024 on the intervention. The company did not identify any studies on the ACT.

For the assessment of the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor, the company transferred the results of RCT VX21-445-124 comparing ivacaftor/tezacaftor/ elexacaftor + ivacaftor with placebo to the given research question. As supporting information, the company took into account the results of 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 RCT VX21-445-124. The company identified the latter 2 studies in its information retrieval in another therapeutic indication (see dossier for benefit assessment A25-61).

The data presented by the company were unsuitable for drawing any conclusions on the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT for the given research question. A detailed rationale is provided below.

Company's approach for transferring the added benefit

The company aimed to transfer the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor from other patient groups to the given research question. The company's reasoning regarding the transfer of the added benefit was primarily based on the results of the randomized, double-blind study VX21-445-124. The study compared ivacaftor/tezacaftor/ elexacaftor + ivacaftor with placebo, each in addition to a basic therapy for cystic fibrosis. The study included patients with cystic fibrosis aged 6 years and older who had at least one ivacaftor/tezacaftor/elexacaftor-responsive CFTR mutation, but no F508del or gating mutation. The company transferred the added benefit both between patients of different age groups and between patients with different mutation types.

For the transferability of the added benefit from patients aged 6 years and older to patients aged 2 to 5 years, the company referred to what it considered to be appropriate comparability

between the age group of 2 to 5 years and older age groups. The company did not present any study results on ivacaftor/tezacaftor/elexacaftor + ivacaftor in patients aged 2 to 5 years.

In its argumentation regarding the transfer of the added benefit between different mutation types, the company took the single-arm observational studies VX22-CFD-016, HEOR-23-445-014, Burgel 2024 and Cromwell 2024 on treatment with ivacaftor/tezacaftor/elexacaftor + ivacaftor into account as supporting information. The company stated in Module 4 B that the registry-based studies VX22-CFD-016, HEOR-23-445-014, Burgel 2024 and Cromwell 2024 showed efficacy comparable to that of study VX21-445-124 across all mutation types, including those not covered by study VX21-445-124 and including common gating mutations. From the company's perspective, it was also shown that the majority of patients whose mutations responded to ivacaftor/tezacaftor elexacaftor in in vitro trials also achieved an improvement in vivo. The company further stated that data from everyday practice showed marked improvements in lung function, growth/weight parameters, sweat chloride concentration and pulmonary exacerbations under treatment with ivacaftor/tezacaftor/ elexacaftor + ivacaftor compared with previous therapy with CFTR modulators, including the ACT ivacaftor. The company added that this indicated the superiority of ivacaftor/tezacaftor/ elexacaftor + ivacaftor over the ACT ivacaftor. According to the company, the extension study VX21-445-125 also showed that the effects described in study VX21-445-124 persisted over 72 weeks.

Added benefit not transferable

Study VX21-445-124, which was the main study used by the company to derive the added benefit, is an RCT comparing ivacaftor/tezacaftor/elexacaftor + ivacaftor versus placebo, plus basic therapy in both study arms. Irrespective of the fact that the patient population included in the study did not correspond to the given research question (at least one non-Class I mutation, including at least one gating mutation and excluding an F508del mutation), ivacaftor was not used as the comparator therapy in the comparator arm in the VX21-445-124 study. Study VX21-445-124 was therefore unsuitable for drawing conclusions on the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor compared with the ACT ivacaftor in patients with cystic fibrosis with at least one non-Class I mutation, including at least one gating mutation and excluding an F508del mutation.

The observational studies VX22-CFD-016, HEOR-23-445-014, Burgel 2024 and Cromwell 2024 as well as the extension study VX21-445-125 used to support the company's argumentation for the transfer of the added benefit between different mutation types are single-arm studies, which do not allow a comparison with the ACT defined by the G-BA. Studies on the ACT are not available. It is not appropriate to consider a pure before-after comparison of the results of treatment with ivacaftor/tezacaftor/elexacaftor + ivacaftor versus prior therapy with CFTR modulators, including ivacaftor, as a sufficient comparison with the ACT ivacaftor.

Results on added benefit

Since no suitable data were available for the benefit assessment, there is no hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 presents a summary of the probability and extent of the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor.

Table 3: Ivacaftor/tezacaftor/elexacaftor + ivacaftor – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Patients with cystic fibrosis aged 2 years and older who have at least one non-Class I mutation, including at least one gating mutation and excluding an F508del mutation, in the CFTR gene	ivacaftor	Added benefit not proven
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

I 2 Research question

The aim of this report is to assess the added benefit of ivacaftor/tezacaftor/elexacaftor in combination with ivacaftor (hereinafter referred to as ivacaftor/tezacaftor/elexacaftor + ivacaftor) in comparison with ivacaftor as the appropriate comparator therapy (ACT) in patients with cystic fibrosis aged 2 years and older who have at least one non-Class I mutation, including at least one gating mutation and excluding an F508del mutation, in the cystic fibrosis transmembrane conductance regulator gene (CFTR).

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of ivacaftor/tezacaftor/elexacaftor + ivacaftor

Therapeutic indication	**ACT[a]**
Patients with cystic fibrosis aged 2 years and older who have at least one non-Class I mutation, including at least one gating mutation and excluding an F508del mutation, in the CFTR gene	ivacaftor
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee	

The company designated ivacaftor as the ACT, thus following the G-BA's specification. The company also stated that, where indicated, patients should additionally be offered symptomatic treatment with both symptomatic drug treatments and non-drug treatment options. This benefit assessment was conducted in comparison with the ACT specified by the G-BA, ivacaftor. An additional symptomatic treatment for the patient population is appropriate.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Studies with a minimum duration of 24 weeks were used for the derivation of the added benefit. This corresponded to the inclusion criteria used by the company for the search for randomized controlled trials (RCTs). Deviating from this, the company did not define a minimum study duration for the search for further studies with the intervention and the ACT. The deviation was of no consequence for this assessment, as the company did not present any suitable data on the comparison of ivacaftor/tezacaftor/elexacaftor + ivacaftor versus the ACT (see Chapter I 3 for details).

I 3 Information retrieval and study pool

The study pool for the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- Study lists on ivacaftor/tezacaftor/elexacaftor + ivacaftor (status: 6 March 2025)
- Bibliographic literature search for ivacaftor/tezacaftor/elexacaftor + ivacaftor (last search on 28 February 2025)
- Search of trial registries/trial results databases for studies on ivacaftor/tezacaftor/elexacaftor + ivacaftor (last search on 28 February 2025)
- Search on the G-BA website for ivacaftor/tezacaftor/elexacaftor + ivacaftor (last search on 11 March 2025)
- Bibliographical literature search on the ACT (last search on 6 March 2025)
- Search of trial registries/trial results databases for studies on the ACT (last search on 28 February 2025)
- Search on the G-BA website for the ACT (last search on 11 March 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on ivacaftor/tezacaftor/elexacaftor + ivacaftor (last search on 19 May 2025); see I Appendix A of the full dossier assessment for the search strategies

Concurring with the company, a review of the completeness of the study pool did not find any RCTs on the direct comparison of ivacaftor/tezacaftor/elexacaftor + ivacaftor versus the ACT ivacaftor in the therapeutic indication in question.

As the company did not identify any RCTs on the direct or adjusted indirect comparison of ivacaftor/tezacaftor/elexacaftor + ivacaftor versus the ACT, it conducted an additional information retrieval for further studies with the intervention and the ACT. In this information retrieval, the company identified the single-arm observational studies VX22-CFD-016 [3], HEOR-23-445-014 [3], Burgel 2024 [4] and Cromwell 2024 [5] on the intervention. The company did not identify any studies on the ACT.

For the assessment of the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor, the company transferred the results of RCT VX21-445-124 comparing ivacaftor/tezacaftor/ elexacaftor + ivacaftor with placebo [6] to the given research question. The study included patients aged 6 years and older who had at least one ivacaftor/tezacaftor/elexacaftor-responsive CFTR mutation, but no F508del or gating mutation (see below). As supporting

information, the company took into account the results of 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 [7] of the RCT VX21-445-124. The company identified the latter 2 studies in its information retrieval in another therapeutic indication (see dossier for benefit assessment A25-61 [8]).

The data presented by the company were unsuitable for drawing any conclusions on the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT for the given research question. A detailed rationale is provided below.

Company's approach for transferring the added benefit

The company aimed to transfer the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor from other patient groups to the given research question. The company's reasoning regarding the transfer of the added benefit was primarily based on the results of the randomized, double-blind study VX21-445-124. A detailed description of the VX21-445-124 study can be found in dossier assessment A25-61 [8]. The study compared ivacaftor/tezacaftor/elexacaftor + ivacaftor with placebo, each in addition to a basic therapy for cystic fibrosis. Patients with cystic fibrosis aged 6 years and older who had at least one ivacaftor/tezacaftor/elexacaftor-responsive mutation on the CFTR gene were included. Patients with at least one of the following mutations were eligible: 2789+5G>A, 3272-26A>G, 3849+10kbC>T, P5L, R117C, L206W, V232D, T338I, R347H, A455E, S945L, L997F, R1066H, D1152H, G85E, R347P, L1077P, M1101K. Neither allele was allowed to have an F508del mutation or a gating mutation (G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R or R117H). The company transferred the added benefit both between patients of different age groups and between patients with different mutation types. Both approaches are discussed in more detail below.

For the transferability of the added benefit from patients aged 6 years and older to patients aged 2 to 5 years, the company referred to the European Medicines Agency (EMA) assessment report on the therapeutic indication of children aged 2 to 5 years with cystic fibrosis with at least one F508del mutation in the CFTR gene [9], based on which it considered there to be appropriate comparability between the age group of 2 to 5 years and older age groups. It based this assumption on a comparable pathophysiology and consistent pharmacokinetic exposure between patients of the different age groups, and on the same mechanism of action in different age groups. The company added that the EMA assessment report on the therapeutic indication of children aged 2 to 5 years with cystic fibrosis with at least one F508del mutation in the CFTR gene [9] assumes comparable efficacy and safety of ivacaftor/tezacaftor/elexacaftor + ivacaftor in different age groups. According to the company, the comparable pharmacokinetic exposure and the common underlying disease process were also decisive for the EMA's assessment of the present therapeutic indication

[10]. The company did not present any study results on ivacaftor/tezacaftor/elexacaftor + ivacaftor in patients aged 2 to 5 years.

In its argumentation regarding the transfer of the added benefit between different mutation types, the company took the single-arm observational studies VX22-CFD-016, HEOR-23-445-014, Burgel 2024 and Cromwell 2024 on treatment with ivacaftor/tezacaftor/elexacaftor + ivacaftor into account as supporting information. The studies VX22-CFD-016 and Cromwell 2024 are both retrospective observational studies based on data from the US Cystic Fibrosis Foundation Patient Registry. The studies included patients with cystic fibrosis aged 6 years and older who had at least one ivacaftor/tezacaftor/elexacaftor-responsive CFTR mutation, excluding an F508del mutation. The HEOR-23-445-014 study retrospectively analysed data from the UK Cystic Fibrosis Registry. Patients with cystic fibrosis aged 6 years and older who did not have an F508del mutation were considered. The Burgel 2024 study is a prospective observational study initiated by the French drug agency, which included patients with cystic fibrosis aged 6 years and older without F508del mutation in the CFTR gene. Patients with a total of 115 non-Class I mutations, including 9 of the 10 gating mutations, were included in the observational studies.

Regarding the transfer of the added benefit between different mutation types, the company stated in Module 4 B that the registry-based studies VX22-CFD-016, HEOR-23-445-014, Burgel 2024 and Cromwell 2024 showed efficacy comparable to that of study VX21-445-124 across all mutation types, including those not covered by study VX21-445-124 and including common gating mutations. From the company's perspective, it was also shown that the majority of patients whose mutations responded to ivacaftor/tezacaftor elexacaftor in in vitro trials also achieved an improvement in vivo. The company further stated that data from everyday practice showed marked improvements in lung function, growth/weight parameters, sweat chloride concentration and pulmonary exacerbations under treatment with ivacaftor/tezacaftor/elexacaftor + ivacaftor compared with previous therapy with CFTR modulators, including the ACT ivacaftor. The company added that this indicated the superiority of ivacaftor/tezacaftor/elexacaftor + ivacaftor over the ACT ivacaftor. According to the company, the extension study VX21-445-125 also showed that the effects described in study VX21-445-124 persisted over 72 weeks. The company did not present any results from the VX21-445-125 study in Module 4 B.

Added benefit not transferable

As described above, study VX21-445-124, which was the main study used by the company to derive the added benefit, is an RCT comparing ivacaftor/tezacaftor/elexacaftor + ivacaftor versus placebo, plus basic therapy in both study arms. Patients aged 6 years and older who did not have an F508del mutation or a gating mutation and at least one of the following mutations in the CFTR gene were included: 2789+5G>A, 3272-26A>G, 3849+10kbC>T, P5L,

R117C, L206W, V232D, T338I, R347H, A455E, S945L, L997F, R1066H, D1152H, G85E, R347P, L1077P, M1101K. Irrespective of the fact that the patient population included in the study did not correspond to the given research question (at least one non-Class I mutation, including at least one gating mutation and excluding an F508del mutation), ivacaftor was not used as the comparator therapy in the comparator arm in the VX21-445-124 study. Study VX21-445-124 was therefore unsuitable for drawing conclusions on the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor compared with the ACT ivacaftor in patients with cystic fibrosis with at least one non-Class I mutation, including at least one gating mutation and excluding an F508del mutation.

The observational studies VX22-CFD-016, HEOR-23-445-014, Burgel 2024 and Cromwell 2024 as well as the extension study VX21-445-125 used to support the company's argumentation for the transfer of the added benefit between different mutation types are single-arm studies, which do not allow a comparison with the ACT defined by the G-BA. Studies on the ACT are not available. It is not appropriate to consider a pure before-after comparison of the results of treatment with ivacaftor/tezacaftor/elexacaftor + ivacaftor versus prior therapy with CFTR modulators, including ivacaftor, as a sufficient comparison with the ACT ivacaftor.

Since overall no data were available that would be suitable for drawing conclusions about the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor versus the ACT in the given therapeutic indication, no further comments will be made on the company's transfer of the added benefit between different age groups and between different mutation types.

I 4 Results on added benefit

No suitable data were available for the assessment of the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT in patients with cystic fibrosis aged 2 years and older who have at least one non-Class I mutation, including at least one gating mutation and excluding an F508del mutation, in the CFTR. There is no hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT is summarized in Table 5.

Table 5: Ivacaftor/tezacaftor/elexacaftor + ivacaftor – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Patients with cystic fibrosis aged 2 years and older who have at least one non-Class I mutation, including at least one gating mutation and excluding an F508del mutation, in the CFTR gene	ivacaftor	Added benefit not proven
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company. The company transferred the results of the RCT VX21-445-124 with patients aged 6 years and older who had at least one ivacaftor/tezacaftor/elexacaftor-responsive CFTR mutation, but no F508del or gating mutation, additionally taking into account single-arm data, to the present therapeutic indication and derived a hint of a non-quantifiable added benefit from this.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 02.09.2024]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://doi.org/10.1002/bimj.201300274.

3. Vertex Pharmaceuticals. Ivacaftor/Tezacaftor/ Elexacaftor (Kaftrio); Dossier zur Nutzenbewertung gemäß § 35a SGB V. 2025: [Soon available at: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1216/#dossier].

4. Burgel PR, Sermet-Gaudelus I, Girodon E et al. The expanded French compassionate programme for elexacaftor-tezacaftor-ivacaftor use in people with cystic fibrosis without a F508del CFTR variant: a real-world study. Lancet Respir Med 2024; 12(11): 888-900. https://doi.org/10.1016/S2213-2600(24)00208-X.

5. Cromwell EA, Ostrenga JS, Sanders DB et al. Impact of the expanded label for elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis with no F508del variant in the USA. Eur Respir J 2024; 64(5). https://doi.org/10.1183/13993003.01146-2024.

6. Vertex Pharmaceuticals. Evaluation of Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor (ELX/TEZ/IVA) in Cystic Fibrosis Subjects Without an F508del Mutation [online]. 2024 [Accessed: 10.06.2025]. URL: https://clinicaltrials.gov/study/NCT05274269?cond=Cystic%20Fibrosis&term=VX21-445-124&rank=1.

7. Vertex Pharmaceuticals. Study to Evaluate Elexacaftor/Tezacaftor/Ivacaftor (ELX/TEZ/IVA) Long-term Safety and Efficacy in Subjects Without F508del [online]. 2025 [Accessed: 16.06.2025]. URL: https://www.clinicaltrials.gov/study/NCT05331183.

8. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Ivacaftor/Tezacaftor/Elexacaftor (Kombination mit Ivacaftor; zystische Fibrose, ≥ 2 Jahre, mindestens 1 Nicht-Klasse-I-Mutation, exklusive F508del- und Gating-Mutation) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. 2025: [Soon available at: https://www.iqwig.de/projekte/a25-61.html].

9. European Medicines Agency. Kaftrio; Assessment report [online]. 2023 [Accessed: 16.06.2025]. URL: https://www.ema.europa.eu/en/documents/variation-report/kaftrio-h-c-005269-x-0033-epar-assessment-report-variation_en.pdf.

10. European Medicines Agency. Kalydeco, Kaftrio; CHMP extension of indication variation assessment report [unpublished]. 2025.

The full report (German version) is published under https://www.iqwig.de/en/projects/a25-62.html.