# Ivacaftor/tezacaftor/elexacaftor (combination with ivacaftor; cystic fibrosis, 2 to 5 years, F508del mutation, other/unknown mutation, heterozygous)

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

**EXTRACT**

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[1] Translation of Sections I 1 to I 6 of the dossier assessment *Ivacaftor/Tezacaftor/Elexacaftor (Kombination mit Ivacaftor; zystische Fibrose, 2 bis 5 Jahre, F508del-Mutation, andere / unbekannte Mutation, heterozygot) – 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.

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

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

**Medical and scientific advice**

- Michael Barker

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

**Patient and family involvement**

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

IQWiG thanks the respondent and the Mukoviszidose e. V. (Cystic Fibrosis Institute) for participating in the written exchange and for their support. The respondent and the Mukoviszidose e. V. were not involved in the actual preparation of the dossier assessment.

**IQWiG employees involved in the dossier assessment**

- Selver Altin
- Kirsten Janke
- Maximilian Kind
- Ulrike Lampert
- Jona Lilienthal
- Prateek Mishra
- Daniela Preukschat
- Min Ripoll

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# 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 |
| BSC | best supportive care |
| CFTR | cystic fibrosis transmembrane conductance regulator |
| ELX | elexacaftor |
| 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) |
| IVA | ivacaftor |
| MF | minimal function |
| PAES | post-approval efficacy study |
| RCT | randomized controlled trial |
| RF | residual function |
| 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 is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 5 December 2023.

### 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 best supportive care (BSC) as the appropriate comparator therapy (ACT) in cystic fibrosis patients 2 to 5 years of age who are heterozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene and have, on the second allele, a mutation other than a minimal function (MF), gating (including R117H mutation), or residual function (RF) mutation or with unknown mutation on the second allele (hereinafter referred to as "other/unknown mutation").

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

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

| **Therapeutic indication** | **ACT[a]** |
|---|---|
| Patients with cystic fibrosis from 2 to 5 years of age who are heterozygous for the F508del mutation in the CFTR gene and have a mutation on the second allele other than an MF, gating (including R117H), or RF mutation, or in whom the mutation on the second allele is unknown | BSC[c] |

a. Presented is the ACT specified by the G-BA.
b. The group of mutations on the second allele is also referred to as "other/unknown mutation".
c. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life (particularly antibiotics for pulmonary infection, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy [within the meaning of the German Remedies Directive] under exhaustion of all possible dietary interventions).

ACT: appropriate comparator therapy; BSC: best supportive care; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee; MF: minimal function; RF: residual function

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

The assessment is 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 added benefit.

**Results**

***Evidence provided by the company***

The check of completeness of the study pool produced no randomized controlled trial (RCT) on a direct comparison of ivacaftor/tezacaftor/elexacaftor + ivacaftor versus the ACT BSC in the present therapeutic indication. Due to the lack of studies of direct comparison, the company carried out an additional information retrieval on non-comparative studies with the intervention, but it did not find any relevant studies. Despite the lack of evidence, the company has claimed an added benefit in the present therapeutic indication by transferring the added benefit established for patients in different age groups who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation on the second allele to the target population of the present therapeutic indication.

The company's approach is unsuitable for drawing any conclusions on the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT for the population of the present research question. This is justified below.

***Company's approach for transferring added benefit***

The company aimed to transfer the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor from other patient groups to the target population relevant for the present research question. For this purpose, the company considered a total of 5 studies.

The company's reasoning is primarily based on the results of the single-arm study VX20-445-111 and the associated extension study VX20-445-112, which were the basis for granting extension of approval of ivacaftor/tezacaftor/elexacaftor + ivacaftor for the present age group of 2 to 5 years. In addition, the company considered RCT VX17-445-102 as well as RCT VX19-445-116 and the single-arm study VX18-445-106. All studies included patients who were heterozygous for the F508del mutation in the CFTR gene and had an MF mutation on the second allele – each in different age groups (2 to 5 years, 6 to 11 years, and 12 years and older). To transfer the added benefit between different mutation types, the company argued in Module 4 E that the effect of ivacaftor/tezacaftor/elexacaftor + ivacaftor treatment is based on the protein product of the CFTR allele with the F508del mutation and is largely independent of the mutation on the second allele of the CFTR gene. The company concluded that results for patients with a heterozygous F508del mutation and an MF mutation on the second allele could be transferred as a "conservative estimate" to patients with a heterozygous F508del mutation and other/unknown mutation on the second allele.

**Added benefit not transferable**

For the therapeutic indication to be assessed, the dossier does not present any studies, neither RCTs nor otherwise, investigating the intervention examined in this benefit assessment. For the transfer of added benefit between different mutation types, the company referred to several

studies, which also included patients with an F508del mutation in the CFTR gene and an MF mutation on the second allele in different age groups. The company made a purely qualitative argument through the principle of action of the intervention rather than submitting any data on patient-relevant outcomes in the patients relevant for the present research question. Transferring study results from patients with heterozygous F508del mutation and an MF mutation on the second allele to the patient group in the present therapeutic indication is consequently impossible on the basis of the information submitted by the company.

**Results on added benefit**

Since no suitable data are 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 shows a summary of the probability and extent of 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 from 2 to 5 years of age who are heterozygous for the F508del mutation in the CFTR gene and have a mutation on the second allele other than an MF, gating (including R117H), or RF mutation, or in whom the mutation on the second allele is unknown | BSC[c] | Added benefit not proven |

a. Presented is the ACT specified by the G-BA.
b. The group of mutations on the second allele is also referred to as “other/unknown mutation”.
c. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life (particularly antibiotics for pulmonary infection, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy [within the meaning of the German Remedies Directive] under exhaustion of all possible dietary interventions).

ACT: appropriate comparator therapy; BSC: best supportive care; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee; MF: minimal function; RF: residual function

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 BSC as the ACT in cystic fibrosis patients 2 to 5 years of age who are heterozygous for the F508del mutation in the CFTR gene and have, on the second allele, a mutation other than an MF, gating (including R117H mutation), or RF mutation or with unknown mutation on the second allele (hereinafter referred to as "other/unknown mutation").

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

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

| **Therapeutic indication** | **ACT**[a] |
|---|---|
| Patients with cystic fibrosis from 2 to 5 years of age who are heterozygous for the F508del mutation in the CFTR gene and have a mutation on the second allele other than an MF, gating (including R117H), or RF mutation, or in whom the mutation on the second allele is unknown | BSC[c] |

a. Presented is the ACT specified by the G-BA.
b. The group of mutations on the second allele is also referred to as "other/unknown mutation".
c. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life (particularly antibiotics for pulmonary infection, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy [within the meaning of the German Remedies Directive] under exhaustion of all possible dietary interventions).

ACT: appropriate comparator therapy; BSC: best supportive care; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee; MF: minimal function; RF: residual function

The company designated BSC as the ACT, thus following the G-BA's specification. According to the company, all cystic fibrosis patients were to receive individualized treatment for the alleviation of symptoms and improvement of quality of life, in addition to treatment with CFTR modulators. This is appropriate.

The assessment is 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 added benefit. This concurs with the company's inclusion criteria.

## I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study lists on ivacaftor/tezacaftor/elexacaftor + ivacaftor (status: 15 September 2023)
- bibliographic literature search for ivacaftor/tezacaftor/elexacaftor + ivacaftor (last search on 5 September 2023)
- search in trial registries/trial results databases for ivacaftor/tezacaftor/elexacaftor + ivacaftor (last search on 5 September 2023)
- search on the G-BA website for ivacaftor/tezacaftor/elexacaftor + ivacaftor (last search on 5 September 2023)

To check the completeness of the study pool:

- search in trial registries for studies on ivacaftor/tezacaftor/elexacaftor + ivacaftor (last search on 18 December 2023); see I Appendix A of the full dossier assessment for the search strategies

Concurring with the company, the check of the completeness of the study pool produced no RCT on the direct comparison of ivacaftor/tezacaftor/elexacaftor + ivacaftor versus the ACT BSC in the present therapeutic indication.

Due to the lack of studies of direct comparison, the company carried out an additional information retrieval on non-comparative studies with the intervention, but it did not find any relevant studies. The company conducted no information retrieval for the ACT.

Despite the lack of evidence, the company has claimed an added benefit in the present therapeutic indication by transferring the added benefit established for patients in different age groups (2 to 5 years, 6 to 11 years, and 12 years and older) who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation on the second allele to the target population of the present therapeutic indication.

The company's approach is unsuitable for drawing any conclusions on the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT for the population of the present research question. This is justified below.

**Company's approach for transferring added benefit**

The company aimed to transfer the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor from other patient groups to the target population relevant for the present research

question. For this purpose, the company considered a total of 5 studies, which included patients with a different mutation type than the target population in various age groups, some of which differed from the target population (2 to 5 years, 6 to 11 years, and 12 years and older).

The company's reasoning is primarily based on the results of the single-arm study VX20-445-111 [3] and the associated extension study VX20-445-112 [4], which were the basis for granting extension of approval of ivacaftor/tezacaftor/elexacaftor + ivacaftor for the present age group of 2 to 5 years. These studies included patients from 2 to 5 years of age who were heterozygous for the F508del mutation in the CFTR gene and had an MF mutation on the second allele, or were homozygous for the F508del mutation. In Module 4 E, the company exclusively presented the results of the VX20-445-111 study (for a subpopulation with an F508del/MF mutation in the CFTR gene). Information on both studies can be found in the dossier assessments for the Commissions A23-122 [5] and A23-123 [6]. The company additionally considered the RCT VX17-445-102 [7], which is described in the dossier assessment for Commission A20-83 [8], as well as the RCT VX19-445-116 [9], and the single-arm study VX18-445-106 [10], which are described in the dossier assessment for the Commissions A22-15 and A22-21 [11]. Each of these studies included patients in an older age group and with a different mutation type than the relevant target population. This includes patients aged 6 to 11 years (VX19-445-116) and patients aged 12 years and older (VX17-445-102) who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation on the second allele, or patients aged 6 to 11 years who are either heterozygous for the F508del mutation in the CFTR gene and have an MF mutation on the second allele or are homozygous for the F508del mutation in the CFTR gene (VX18-445-106).

To transfer the added benefit between different mutation types, the company argued in Module 4 E that the effect of ivacaftor/tezacaftor/elexacaftor + ivacaftor treatment is based on the protein product of the CFTR allele with the F508del mutation and is largely independent of the mutation on the second allele of the CFTR gene. The company concluded that results for patients with a heterozygous F508del mutation and an MF mutation on the second allele could be transferred as a "conservative estimate" to patients with a heterozygous F508del mutation and other/unknown mutation on the second allele. The company argued that, while the target population's response in the present therapeutic indication can be quite heterogeneous, results for patients with heterozygous F508del mutation and an MF mutation on the second allele represent the least favourable case in ivacaftor/tezacaftor/elexacaftor + ivacaftor therapy, and therefore, the efficacy of the intervention on the protein product of the CFTR allele with other/unknown mutation should largely exceed the efficacy on the protein product of the CFTR allele with an MF mutation. Furthermore, the company cited the broad approval for ivacaftor/tezacaftor/elexacaftor + ivacaftor for all patients with at least one F508del mutation in the CFTR gene and the evaluation by clinical experts.

**Added benefit not transferable**

Since the dossier does not contain any studies, neither RCTs nor other studies, with the intervention considered in the present benefit assessment for the therapeutic indication to be assessed, a comparison with a different age group or with a different mutation type is not possible. Furthermore, the dossier does not include any studies or other information for evaluating the course of disease under the ACT BSC for the therapeutic indication to be assessed.

For the transfer of added benefit between different mutation types, the company referred to several studies (VX20-445-111, VX20-445-112, VX17-445-102, VX19-445-116 and VX18-445-106), which also included patients with an F508del mutation in the CFTR gene and an MF mutation on the second allele in different age groups. The company made a purely qualitative argument through the principle of action of the intervention rather than submitting any data on patient-relevant outcomes in the patients relevant for the present research question. Transferring study results from patients with heterozygous F508del mutation and an MF mutation on the second allele to the patient group in the present therapeutic indication is consequently impossible on the basis of the information submitted by the company.

Furthermore, in Module 3 E of the dossier, the company itself described that patients in the present therapeutic indication may exhibit one of many different mutations on the second allele. The company conceded that the respective mutation can affect the formed CFTR protein and its response to CFTR modulation in different ways, resulting in substantial heterogeneity in the clinical picture of these patients. On this basis, it remains unclear to what extent the target population relevant in the present therapeutic indication with diverse mutations on the second allele of the CFTR gene can be compared with patients who have only an MF mutation on the second allele of the CFTR gene.

The European Medicines Agency (EMA) also noted in the context of the extension of approval [12] that the data situation for patients aged 2 to 5 years who are heterozygous for the F508del mutation in the CFTR gene is insufficient and that there are uncertainties regarding the optimal age to start treatment with ivacaftor/tezacaftor/elexacaftor + ivacaftor. The company was therefore requested by the EMA to collect comparative evidence for patients aged 2 to 5 years with heterozygous F508del mutation in the CFTR gene as part of a post-approval efficacy study (PAES). The corresponding study protocol is to be submitted to the EMA by June 2024, with the final report expected in December 2029 [12].

## I 4 Results on added benefit

No suitable data are available for assessing the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT in cystic fibrosis patients 2 to 5 years of age who are heterozygous for the F508del mutation in the CFTR gene and have, on the second allele, a mutation other than an MF, gating (including R117H mutation), or RF mutation or with unknown mutation on the second allele. There is no hint of 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

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

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 from 2 to 5 years of age who are heterozygous for the F508del mutation in the CFTR gene and have a mutation on the second allele other than an MF, gating (including R117H), or RF mutation, or in whom the mutation on the second allele is unknown | BSC[c] | Added benefit not proven |

a. Presented is the ACT specified by the G-BA.
b. The group of mutations on the second allele is also referred to as “other/unknown mutation”.
c. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life (particularly antibiotics for pulmonary infection, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy [within the meaning of the German Remedies Directive] under exhaustion of all possible dietary interventions).

ACT: appropriate comparator therapy; BSC: best supportive care; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee; MF: minimal function; RF: residual function

The above assessment departs from the assessment by the company, which transferred the added benefit established in patients in different age groups with heterozygous F508del mutation and an MF mutation on the second allele to the present therapeutic indication, claiming a hint of non-quantifiable added benefit.

The G-BA decides on the added benefit.

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Please see full dossier assessment for full reference list.

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