IQWiG Reports – Commission No. A21-71

# Ivacaftor/tezacaftor/elexacaftor (combination with ivacaftor; cystic fibrosis, 12 years and older, F508del mutation, gating mutation, heterozygous) –

## Benefit assessment according to §35a Social Code Book V[1]

## Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Ivacaftor/Tezacaftor/Elexacaftor (Kombination mit Ivacaftor; zystische Fibrose, ab 12 Jahre, F508del-Mutation, Gating-Mutation, heterozygot) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 August 2021). Please note: This document was translated by an external translator and 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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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

**List of abbreviations**

| Abbreviation | Meaning |
|---|---|
| ACT | appropriate comparator therapy |
| CFTR | cystic fibrosis transmembrane conductance regulator |
| FEV1 | forced expiratory volume in 1 second |
| 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) |

# 2 Benefit assessment

## 2.1 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 27 May 2021.

### 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 the appropriate comparator therapy (ACT) in cystic fibrosis (CF) patients aged 12 years or older who are heterozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene and have a gating mutation (including R117H mutation) on the 2nd allele.

The G-BA's specification of the ACT results in the research question presented in Table 2.

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

| Indication | ACT[a] |
|---|---|
| CF patients aged 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and have a gating mutation (including R117H) on the 2nd allele. | Ivacaftor |
| a. Presented is the ACT specified by the G-BA.<br>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 reports that the ACT as well as the drug to be assessed were administered in addition to the best available individualized symptomatic treatment. This benefit assessment was conducted in comparison with the ACT specified by the G-BA, ivacaftor. Providing 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 submitted by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of added benefit.

**Evidence provided by the company**

***VX18-445-104 study***

In its dossier, the company used the VX18-445-104 study for assessing the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with ivacaftor. This double-blind RCT included CF patients aged 12 years and older who had a heterozygous F508del mutation in the CFTR gene. The 2nd allele had to have either a gating mutation (including the R117H mutation) or a residual function mutation. Depending on the type of mutation, the comparator therapy was either ivacaftor (gating mutations) or tezacaftor/ivacaftor + ivacaftor (residual function mutations). At screening, patients also had to have a forced expiratory volume in 1 second (FEV1) ≥ 40% and ≤ 90% of predicted normal for age, sex, and height. For the present benefit assessment, the subpopulation with a gating mutation (including R117H mutation) on the 2nd allele is relevant.

The study consisted of a 28-day run-in phase, followed by an 8-week treatment phase and a 28-day follow-up observation phase. Following the treatment phase, an open-label extension study was available.

***Insufficient study duration***

Due to a study duration of only 8 weeks, the VX18-445-104 study submitted by the company is unsuitable for a benefit assessment in the therapeutic indication of CF – a chronic disease requiring lifelong treatment. No conclusions can be drawn on the basis of short-term studies as to whether short-term effects will persist over a longer period. Additionally, it is impossible to record any effects that become apparent only in the longer term, e.g. for pulmonary exacerbations and their consequences or for adverse events.

Overall, studies of at least 24 weeks' duration are necessary to compare benefit and harm in benefit assessments in the therapeutic indication of CF. However, due to the rarity of the mutations to be investigated and the fact that children are affected in this therapeutic indication, the VX18-445-104 study and the corresponding short-term results are presented as supplementary information in the appendix of the dossier assessment. No conclusion on added benefit is derived from them.

**Results on added benefit**

No suitable data are available for assessing the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor versus the ACT in CF patients aged 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and have a gating mutation (including R117H) on the 2nd allele. Consequently, there is no hint of any 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

| Indication | ACT[a] | Probability and extent of added benefit |
|---|---|---|
| CF patients aged 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and have a gating mutation (including R117H) on the 2nd allele. | 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].

## 2.2 Research question

The aim of this report is to assess the added benefit of ivacaftor/tezacaftor/elexacaftor in combination with ivacaftor (ivacaftor/tezacaftor/elexacaftor + ivacaftor) in comparison with the ACT in CF patients aged 12 years or older who are heterozygous for the F508del mutation in the CFTR gene and have a gating mutation (including R117H mutation) on the 2nd allele.

The G-BA's specification of the ACT results in the research question presented in Table 4.

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

| **Indication** | **ACT[a]** |
|---|---|
| CF patients aged 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and have a gating mutation (including R117H) on the 2nd allele. | Ivacaftor |
| a. Presented is the ACT specified by the G-BA.<br>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 reported that the ACT ivacaftor as well as the drug to be assessed, ivacaftor/tezacaftor/elexacaftor + ivacaftor, were administered in addition to the best available individualized symptomatic therapy. This benefit assessment was conducted in comparison with the ACT specified by the G-BA, ivacaftor. Providing 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 submitted by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of added benefit. This deviates from the company's inclusion criteria, which specified a minimum study duration of 8 weeks.

## 2.3 Information retrieval and study pool

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

Sources cited by the company in the dossier:

- study list on ivacaftor/tezacaftor/elexacaftor + ivacaftor (status: 15 March 2021)
- bibliographic literature search on ivacaftor/tezacaftor/elexacaftor + ivacaftor (most recent search on 15 March 2021)
- search in trial registries / study results databases on ivacaftor/tezacaftor/elexacaftor + ivacaftor (most recent search on 15 March 2021)
- search on the G-BA website for ivacaftor/tezacaftor/ivacaftor + ivacaftor (most recent search on 15 March 2021)

The company's search strategies are documented in the dossier.

To check the completeness of the study pool:

- Search in trial registries for studies on ivacaftor/tezacaftor/elexacaftor (most recent search on 14 March 2021); see Appendix B of the full dossier assessment for the search strategies.

No relevant study was identified from the check.

**Evidence provided by the company**

***VX18-445-104 study***

In its dossier, the company used the VX18-445-104 study [3-5] for the assessment of added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with ivacaftor. This double-blind RCT included CF patients aged 12 years and older who had a heterozygous F508del mutation in the CFTR gene. The 2nd allele had to have either a gating mutation (including the R117H mutation) or a residual function mutation. Depending on the type of mutation, the comparator therapy was either ivacaftor (gating mutations) or tezacaftor/ivacaftor + ivacaftor (residual function mutations). At screening, patients additionally had to exhibit an FEV1 ≥ 40% and ≤ 90% of predicted normal for age, sex, and height. In the present assessment, the subpopulation with a gating mutation (including R117H mutation) on the 2nd allele corresponds to the therapeutic indication to be assessed. From this subpopulation, 50 patients were randomly allocated to the study's intervention arm and 45 to the control arm.

The study consisted of a 28-day run-in phase, followed by an 8-week treatment phase and a 28-day follow-up observation phase. Following the treatment phase, an open-label extension study was available. During the run-in phase, all patients received 150 mg IVA twice daily. While in the control arm, this treatment was continued after randomization, patients in the intervention arm switched to treatment with ivacaftor/tezacaftor/elexacaftor (150/100/200 mg)

in the morning in combination with 150 mg ivacaftor in the evening. The study protocol specified for the individual patients' pretreatment to be continued at a stable dose. However, Module 4 C reveals that individualized adjustments were made in some cases. Treatment with ivacaftor/tezacaftor/elexacaftor or ivacaftor was administered in compliance with the Summary of Product Characteristics [6,7].

The primary outcome of the study was percent change in FEV1 from baseline. Patient-relevant secondary outcomes were symptoms, health-related quality of life, and adverse events.

***Insufficient study duration***

Due to a study duration of only 8 weeks, the VX18-445-104 study submitted by the company is unsuitable for a benefit assessment in the therapeutic indication of CF – a chronic disease requiring lifelong treatment. The European Medicines Agency (EMA) guideline recommends a minimum duration of 6 months for the investigation of a clinical outcome [8]. IQWiG's General Methods 6.0 also consider long-term studies to be necessary for the benefit assessment of chronic diseases [1]. In the therapeutic indication of CF, short-term studies (with a treatment duration of less than 24 weeks) are unsuitable for the benefit assessment since ivacaftor/tezacaftor/elexacaftor in combination with ivacaftor is a long-term treatment. No conclusions can be drawn on the basis of short-term studies as to whether short term effects persist in the longer term. Additionally, it impossible to record any effects that become apparent only in the longer term, e.g. for pulmonary exacerbations and their consequences or for adverse events. In Module 4 C, the company justified its inclusion criterion of 8 weeks by arguing that this had been the maximum treatment duration of the only randomized study in the therapeutic indication. The company's rationale was not found plausible.

Overall, studies of at least 24 weeks' duration are necessary to compare benefit and harm in the benefit assessment for the therapeutic indication of CF. However, due to the rarity of the mutations to be investigated and the fact that children are affected in the present therapeutic indication, the VX18-445-104 study and the corresponding short-term results are presented as supplementary information in the appendix of the present dossier assessment (see Appendix A). No conclusion on added benefit is derived from them.

## 2.4 Results on added benefit

No suitable data are available for assessing the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor versus the ACT in CF patients aged 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and have a gating mutation (including R117H) on the 2nd allele. Consequently, 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.

## 2.5 Probability and extent of added benefit

Table 5 presents a summary of the results of the benefit assessment of ivacaftor/tezacaftor/ elexacaftor + ivacaftor in comparison with the ACT.

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

| **Indication** | **ACT**[a] | **Probability and extent of added benefit** |
|---|---|---|
| CF patients aged 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and have a gating mutation (including R117H) on the 2nd allele. | Ivacaftor | Added benefit not proven |
| a. Presented is the ACT specified by the G-BA.<br>ACT: appropriate comparator therapy; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee | | |

The assessment described above deviates from that by the company, which derived an indication of considerable added benefit on the basis of the VX18445-104 study.

The G-BA decides on the added benefit.

**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.

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