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Ivacaftor/tezacaftor/elexacaftor and ivacaftor (cystic fibrosis, 6 to 11 years, F508del and other/unknown mutations, 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 und Ivacaftor (zystische Fibrose, 6 bis 11 Jahre, F508del-Mutation, andere / unbekannte Mutation, heterozygot) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 May 2022). 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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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

No feedback was received in the framework of the present dossier assessment.

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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
BSC	best supportive care
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MF	minimal function
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 combination of ivacaftor/tezacaftor/elexacaftor plus ivacaftor as well as the benefit assessment of the drug combination of ivacaftor plus ivacaftor/tezacaftor/elexacaftor. 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 8 February 2022.

Research question

The aim of this report is to assess the added benefit of ivacaftor/tezacaftor/elexacaftor in combination with ivacaftor (hereinafter ivacaftor/tezacaftor/elexacaftor + ivacaftor) versus best supportive care (BSC) as the appropriate comparator therapy (ACT) in patients ages 6 to 11 years with cystic fibrosis (CF) who are heterozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene and have, on the 2nd allele, a mutation other than a minimal function (MF), gating (including R117H mutation), or residual function (RF) mutation or who have an unknown mutation on the 2nd allele (hereinafter "other/unknown mutation").

The research question presented in Table 2 results 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]**
CF patients ages 6 to 11 years who are heterozygous for the F508del mutation in the CFTR gene and have a mutation on the 2nd allele[b] other than an MF, gating (including R117H), or RF mutation or in whom the mutation on the 2nd allele is unknown	BSC[c]

a. Presented is the ACT specified by the G-BA.
b. The group of mutations on the 2nd allele is also referred to as "other/unknown mutation".
c. BSC refers to the therapy that 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 "Heilmittel Richtlinie", Germany's Remedies Directive] under exhaustion of all possible dietary interventions).

ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; 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 was conducted by means of patient-relevant outcomes on the basis of the data provided 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.

Results

Evidence provided by the company

The check of completeness of the study pool produced no RCTs on the direct comparison of ivacaftor/tezacaftor/elexacaftor + ivacaftor versus the ACT. Due to a lack of directly comparative studies, the company carried out an additional information procurement on further investigations 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 taking the added benefit for patients of the same age group but with a different mutation type and transferring said benefit 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 of BSC. A rationale is provided below.

Company's approach for transferring added benefit

The company aims to transfer the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor to the target population relevant for the present therapeutic indication based on a discussion of the transferability of study results between patients in the target population's age group with different mutation types. For this purpose, the company's argumentation cites results from studies including patients ages 6 to 11 years with mutation types other than those of the target population (including heterozygous for the F508del mutation in the CFTR gene with MF mutation on the 2nd allele [VX19-445-116]). As a central argument in its discussion regarding the transferability of added benefit between different mutation types, the company contends that the effect of ivacaftor/tezacaftor/elexacaftor + ivacaftor treatment is based on the protein product of the CFTR allele with F508del mutation and is largely independent of the mutation on the CFTR gene's 2nd allele.

Added benefit not transferable

For the therapeutic indication to be assessed, the dossier does not present any studies, whether RCTs or otherwise, investigating the intervention examined in this benefit assessment. Regarding the transferability of added benefit between different mutation types, the company makes 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. Consequently, despite a shared ACT, transferring study results from patients with a different mutation type to the patient group in the present therapeutic indication is impossible on the basis of the information submitted by the company.

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 CF patients ages 6 to 11 years who are heterozygous for the F508del mutation in the CFTR gene and have a 2nd allele mutation other than an MF, gating (including R117H), or RF mutation or in whom the mutation on the second allele is unknown. Consequently, there is no hint of 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
CF patients ages 6 to 11 years who are heterozygous for the F508del mutation in the CFTR gene and have a mutation on the 2nd allele[b] other than an MF, gating (including R117H), or RF mutation or in whom the mutation on the 2nd 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 2nd allele is also referred to as "other/unknown mutation".
c. BSC refers to the therapy that 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 "Heilmittel Richtlinie", Germany's Remedies Directive] under exhaustion of all possible dietary interventions).

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

The result of this benefit assessment equally applies to ivacaftor in combination with ivacaftor/tezacaftor/elexacaftor.

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 (hereinafter ivacaftor/tezacaftor/elexacaftor + ivacaftor) in comparison with BSC as the ACT in CF patients ages 6 to 11 years who are heterozygous for the F508del mutation in the CFTR gene and have, on the 2nd allele, a mutation other than an MF, gating (including R117H mutation), or RF mutation or with unknown mutation on the 2nd allele (hereinafter "other/unknown mutation").

The research question presented in Table 4 results 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]**
CF patients ages 6 to 11 years who are heterozygous for the F508del mutation in the CFTR gene and have a mutation on the 2nd allele[b] other than an MF, gating (including R117H), or RF mutation or in whom the mutation on the 2nd allele is unknown	BSC[c]

a. Presented is the ACT specified by the G-BA.
b. The group of mutations on the 2nd allele is also referred to as "other/unknown mutation".
c. BSC refers to the therapy that 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 "Heilmittel Richtlinie", Germany's Remedies Directive] under exhaustion of all possible dietary interventions).

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

The company has named BSC as ACT and thus followed the G-BA's specification. The company additionally reports that all CF 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 was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of added benefit. This concurs with the company's inclusion criteria.

2.3 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 list on ivacaftor/tezacaftor/elexacaftor + ivacaftor (status: 15 November 2021)
- bibliographic literature search on ivacaftor/tezacaftor/elexacaftor + ivacaftor (last search on 15 November 2021)

- search in trial registries / study results databases on ivacaftor/tezacaftor/elexacaftor + ivacaftor (last search on 15 November 2021)
- search on the G-BA website for ivacaftor/tezacaftor/ivacaftor + ivacaftor (last search on 15 November 2021)

To check the completeness of the study pool:

- Search in trial registries for studies on ivacaftor/tezacaftor/elexacaftor + ivacaftor (last search on 24 February 2022); see Appendix A of the full dossier assessment for the search strategies.

Concurring with the company, the check of completeness of the study pool produced no RCTs on the direct comparison of ivacaftor/tezacaftor/elexacaftor + ivacaftor versus the ACT.

Due to a lack of directly comparative studies, the company carried out an additional information procurement on further investigations with the intervention, but it did not find any relevant studies.

Despite a lack of evidence, the company claims an added benefit in the present therapeutic indication by taking the added benefit from CF patients ages 6 to 11 years who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation on the 2nd allele and transferring said added benefit to the target population in the present benefit assessment.

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

Company's approach for transferring added benefit

The company aims to transfer the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor to the target population relevant for the present therapeutic indication based on a discussion of the transferability of study results between patients in the target population's age group with different mutation types. For this purpose, the company's arguments include the results of the RCT VX19-445-116 [3], the single-arm study VX18-445-106 [4], and the associated extension study VX19-445-107 [5]. The company refers to results on these studies, which it presents in the dossier's Module 4 A and Module 4 B. Each of these studies included CF patients ages 6 to 11 years with mutation types other than those of the target population: heterozygous for the F508del mutation in the CFTR gene and an MF mutation on the 2nd allele (VX19-445-116) or either an MF mutation on the 2nd allele or homozygous for the F508del mutation in the CFTR gene (VX18-445-106 and VX19-445-107). Detailed information on the RCT VX19-445-116 can be found in the dossier assessments on Commissions A22-15 and A22-21 [6].

In its discussion of the transferability of added benefit, the company argues 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 2nd allele of the CFTR gene. The company maintains that study results for patients with heterozygous F508del mutation and an MF mutation on the 2nd allele can be transferred as a "conservative estimate" to patients with at least one F508del mutation because the protein product of the CFTR allele with the MF mutation is not affected by ivacaftor/tezacaftor/elexacaftor + ivacaftor treatment. The company argues 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 2nd allele represent the least favourable case in ivacaftor/tezacaftor/elexacaftor + ivacaftor therapy, and therefore, the effectiveness of the intervention in patients with a different or unknown mutation should largely exceed effectiveness in patients with MF mutation on the 2nd allele. Furthermore, the company cites (1) the broad approval for ivacaftor/tezacaftor/elexacaftor + ivacaftor for all patients with at least one F508del mutation, (2) clinical studies on the intervention in patients aged 12 years and older, and (3) evaluation by clinical experts.

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. Furthermore, the dossier does not include any studies or other information for evaluating the course of disease under BSC for the therapeutic indication in question. Regarding the transferability of added benefit between different mutation types, the company makes 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 2nd allele to the patient group in the present therapeutic indication is consequently impossible on the basis of the information submitted by the company, despite the identical ACT.

Furthermore, in Module 3 E of the dossier, the company mentions that patients in the present therapeutic indication may exhibit 1 of many different mutations on the 2nd allele. The company concedes 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 2nd allele of the CFTR gene can be compared with patients who have only an MF mutation on the 2nd allele of the CFTR gene.

2.4 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 CF patients ages 6 to 11 years who are heterozygous for the F508del mutation in the CFTR gene and have a 2nd allele mutation other than an MF, gating (including R117H), or RF mutation or in whom the mutation on the second allele is

unknown. Consequently, there is no hint of 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 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**
CF patients ages 6 to 11 years who are heterozygous for the F508del mutation in the CFTR gene and have a mutation on the 2nd allele[b] other than an MF, gating (including R117H), or RF mutation or in whom the mutation on the 2nd 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 2nd allele is also referred to as "other/unknown mutation".
c. BSC refers to the therapy that 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 "Heilmittel Richtlinie", Germany's Remedies Directive] under exhaustion of all possible dietary interventions).

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

The result of this benefit assessment equally applies to ivacaftor in combination with ivacaftor/tezacaftor/elexacaftor.

The above assessment departs from the assessment by the company, which took the added benefit established in patients in the same age group with heterozygous F508del mutation and an MF mutation on the 2nd allele and transferring said added benefit to the present therapeutic indication, claiming an indication of nonquantifiable added benefit.

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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The full report (German version) is published under https://www.iqwig.de/en/projects/a22-19.html.