Ivacaftor/tezacaftor/elexacaftor (combination with ivacaftor; cystic fibrosis, 2 to 5 years, F508del mutation, gating 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, Gating-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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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.

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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
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
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 ivacaftor 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 a gating mutation (including R117H mutation) on the second allele.

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 gating mutation (including R117H) on the second allele	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 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 ivacaftor 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 aged 12 years and older with the same mutation type or patients in different age groups with a different mutation type 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 6 studies.

For the transfer of the added benefit between different age groups, the company considered the RCT VX18-445-104. In the company's view, it was possible to prove the efficacy of the triple combination for patients aged 12 years and older with a heterozygous F508del mutation on the CFTR gene and a gating mutation on the second allele based on the results of study VX18-445-104. On the basis of this RCT, the company claimed a transfer of the added benefit from older to younger patients with the same mutation type.

The company's reasoning regarding the transfer of added benefit between different mutation types 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 its reasoning regarding the transfer of added benefit between different mutation types, the company additionally considered the 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 a minimal function (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 C 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 a gating mutation on the second allele.

Added benefit not transferable

Neither for the intervention nor for the ACT are data available for the target population in the present therapeutic indication. Irrespective of whether the transferability of the results from older patients to the age group of children aged 2 to 5 years is possible in the present therapeutic indication, the added benefit was already assessed as not proven for the older age groups with the mutation type of the present research question, as no suitable data were available. Furthermore, regarding the transfer of added benefit between the different mutation types, the company made a purely qualitative argument through the principle of action of the intervention rather than submitting any data on patient-relevant outcomes for the patients relevant in the present research question. All in all, neither from older patients nor from patients with a different mutation type is it possible to transfer added benefit to the population in the present therapeutic indication on the basis of the information supplied by the company. Therefore, the data presented by the company are unsuitable for drawing conclusions on the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT in the present therapeutic indication.

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 summarizes the probability and extent of added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor.

[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].

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 gating mutation (including R117H) on the second 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.

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 ACT in cystic fibrosis patients 2 to 5 years of age who are heterozygous for the F508del mutation in the CFTR gene and have a gating mutation (including R117H mutation) on the second allele.

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 gating mutation (including R117H) on the second allele	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 additionally reported that the ACT of ivacaftor as well as the drug to be assessed, ivacaftor/tezacaftor/elexacaftor + ivacaftor, were used in addition to individualized therapy to alleviate symptoms and improve the quality of life as in best supportive care. This benefit assessment is conducted in comparison with the ACT specified by the G-BA, ivacaftor. Providing additional symptomatic treatment for the patient population 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 deviates from the company's inclusion criteria, which specified a minimum study duration of 8 weeks. This deviation is of no consequence for the present assessment, as the company did not present any data on the comparison of ivacaftor/tezacaftor/elexacaftor + ivacaftor with the ACT (for reasons, see Chapter I 3).

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 ivacaftor 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 added benefit from the following patient groups to the target population of the present therapeutic indication:

- Patients aged 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and have a gating mutation on the second allele (transfer of added benefit between different age groups)
- 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 (transfer of added benefit between different mutation types)

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 6 studies, which included either patients in a different age group (12 years and older) and with the same mutation type, or 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). Both approaches are discussed in more detail below.

For the transfer of added benefit between different age groups, the company considered the RCT VX18-445-104 [3], which is described in the dossier assessment on Commission A21-71 [4]. This study included patients aged 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and have a gating mutation (including R117H mutation) on the second allele. The company cited the results of this study, arguing that ivacaftor/tezacaftor/elexacaftor + ivacaftor was superior to ivacaftor monotherapy in selected morbidity outcomes. In the company's view, it was possible to prove the efficacy of the triple combination for patients aged 12 years and older with a heterozygous F508del mutation on the CFTR gene and a gating mutation on the second allele based on the results of study VX18-445-104. On the basis of this RCT, the company claimed a transfer of the added benefit from older to younger patients with the same mutation type.

The company's reasoning regarding the transfer of added benefit between different mutation types is primarily based on the results of the single-arm study VX20-445-111 [5] and the associated extension study VX20-445-112 [6], 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 C, 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 [7] and A23-123 [8]. In its reasoning regarding the transfer of added benefit between different mutation types, the company additionally considered the RCT VX17-445-102 [9], which is described in the dossier assessment for Commission A20-83 [10], as well as the RCT VX19-445-116 [11], and the single-arm study VX18-445-106 [12], which are described in the dossier assessment for the Commissions A22-15 and A22-21 [13]. 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 C 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 a gating mutation on the second allele. It argued that the response of the protein product of the gating mutation allele to ivacaftor was maintained and the effect of the triple combination on the protein product of the allele with the F508del mutation was added, resulting in a greater treatment effect. 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 of ivacaftor monotherapy for the therapeutic indication to be assessed.

For the transfer of the added benefit between different age groups with the same mutation type, the company referred exclusively to the VX18-445-104 study. Based on this study, the added benefit for patients aged 12 years and older with a heterozygous F508del mutation in the CFTR gene and a gating mutation on the second allele was already assessed as not proven in dossier assessment A21-71 [4]. For patients aged 6 to 11 years with the same mutation type, the added benefit was also assessed as not proven in the dossier assessment for Commissions A22-17 and A22-23, as no suitable data were available [14]. Thus, irrespective of whether the transferability of the results from older patients to the age group of children aged 2 to 5 years is possible in the present therapeutic indication, the added benefit was assessed as not proven for the older age groups (6 to 11 years, and 12 years and older) with the mutation type of the present research question, as no suitable data were available. It is therefore not possible to transfer the added benefit between different age groups.

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. Consequently, it is impossible to transfer study results from patients with different mutation types to the patient group in the present therapeutic indication on the basis of the information submitted by the company.

Summary

Neither for the intervention nor for the ACT are data available for the target population in the present therapeutic indication. Irrespective of whether the transferability of the results from older patients to the age group of children aged 2 to 5 years is possible in the present therapeutic indication, the added benefit was already assessed as not proven for the older age groups with the mutation type of the present research question, as no suitable data were available. Furthermore, regarding the transfer of added benefit between the different mutation types, the company made a purely qualitative argument through the principle of action of the intervention rather than submitting any data on patient-relevant outcomes for the patients relevant in the present research question. All in all, neither from older patients nor from patients with a different mutation type is it possible to transfer added benefit to the population in the present therapeutic indication on the basis of the information supplied by the company. Therefore, the data presented by the company are unsuitable for drawing conclusions on the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT in the present therapeutic indication.

The European Medicines Agency (EMA) also noted in the context of the extension of approval [15] 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 [15].

I 4 Results on added benefit

No suitable data are available for assessing the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor versus the ACT in cystic fibrosis patients aged 2 to 5 years who are heterozygous for the F508del mutation in the CFTR gene and have a gating mutation (including the R117H 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 gating mutation (including R117H) on the second 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 above assessment departs from the assessment by the company, which transferred the added benefit from patients aged 12 years and older with the same mutation type as the target population and from 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.

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.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a23-124.html.