IQWiG Reports – Commission No. A22-18, A22-24

Ivacaftor/tezacaftor/elexacaftor and ivacaftor (cystic fibrosis, 6 to 11 years, F508del mutation, RF 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 und Ivacaftor (zystische Fibrose, 6 bis 11 Jahre, F508del-Mutation, RF-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.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Ivacaftor/tezacaftor/elexacaftor and ivacaftor (cystic fibrosis, 6 to 11 years, F508del mutation, RF mutation, heterozygous) – Benefit assessment according to §35a Social Code Book V

Commissioning agency

Federal Joint Committee

Commission awarded on

12 February 2022

Internal Commission No.

A22-18, A22-24

Address of publisher

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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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Keywords: Ivacaftor, Tezacaftor, Elexacaftor, Cystic fibrosis, Child, Benefit 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
RF	residual function
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 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 10 February 2022.

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 tezacaftor/ivacaftor in combination with ivacaftor (hereinafter referred to as tezacaftor/ivacaftor + ivacaftor) as the appropriate comparator therapy (ACT) in cystic fibrosis (CF) patients 6 to 11 years of age who are heterozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene and have a residual function (RF) mutation on the 2nd allele.

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 6 to 11 years of age who are heterozygous for the F508del mutation in the CFTR gene and have an RF mutation on the 2nd allele	Tezacaftor/ivacaftor in combination with ivacaftor
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee; RF: residual function	

The company designated tezacaftor/ivacaftor + 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. 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 for a 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 retrieval on other 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 transferring the added benefit established for patients of the same age group but with a different mutation type or from older patients with the same 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. 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 regarding the transferability of study results from patients in the target population's age group but with different mutation types as well as from patients aged 12 years and older with the target population's mutation type.

The company's reasoning regarding the transferability of added benefit from different mutation types cites results from studies on 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 minimal function (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.

The company's reasoning regarding the transferability of added benefit between different age groups with the same mutation type is largely based on results of the VX18-445-104 RCT from the previously assessed therapeutic indication with patients aged 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and have an RF mutation on the 2nd allele. In the company's opinion, the effectiveness of the triple combination in patients aged 12 years and older with an RF mutation on the 2nd allele has been proven by the results of the VX18-445-104 study.

No transferability of added benefit

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. Regarding the transfer 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, it is impossible to transfer study results from patients with a

different mutation type to the patient group in the present therapeutic indication on the basis of the information submitted by the company.

Furthermore, the company's reasoning regarding the transferability of added benefit between different mutation types is based, in part, on results from the VX19-445-116 RCT, for which a different ACT was specified. Hence, a key criterion for transferring results from this study to the population in the present therapeutic indication is not met.

The determinative study VX18-445-104 on which the company bases its reasoning regarding the transferability of added benefit from patients aged 12 years and older has already been deemed unsuitable due to its short study duration in the context of the dossier assessment on this age group (dossier assessments A21-72 and A21-75), and added benefit was deemed not proven for this age group. Hence, irrespective of the transferability of results from patients ages 12 years and older to the age group in the present therapeutic indication, no relevant results are available for patients in either of the 2 age groups who are heterozygous for the F508del mutation and have an RF mutation on the 2nd allele.

All in all, neither from patients with a different mutation type nor from older patients 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.

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 6 to 11 years who are heterozygous for the F508del mutation in the CFTR gene and have an RF mutation on the 2nd allele. 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.

[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**
CF patients from 6 to 11 years of age who are heterozygous for the F508del mutation in the CFTR gene and have an RF mutation on the 2nd allele	Tezacaftor/ivacaftor in combination with ivacaftor	Added benefit not proven
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee; 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.

2.2 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 tezacaftor/ivacaftor in combination with ivacaftor (hereinafter referred to as tezacaftor/ivacaftor + ivacaftor) as the ACT in CF patients 6 to 11 years of age who are heterozygous for the F508del mutation in the CFTR gene and have an RF mutation on the 2nd allele.

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 from 6 to 11 years of age who are heterozygous for the F508del mutation in the CFTR gene and have an RF mutation on the 2nd allele	Tezacaftor/ivacaftor in combination with ivacaftor
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee; RF: residual function	

The company designated tezacaftor/ivacaftor + ivacaftor as the ACT, thus following the G-BA's specification. The company additionally reports that the ACT of tezacaftor/ivacaftor + ivacaftor as well as the drug to be assessed, ivacaftor/tezacaftor/elexacaftor + ivacaftor, was used in addition to individualized therapy to alleviate symptoms and improve the quality of life within the meaning of best supportive care (BSC). The present benefit assessment was conducted in comparison with tezacaftor/ivacaftor + ivacaftor, the ACT specified by the G-BA. 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 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 directly comparing ivacaftor/tezacaftor/elexacaftor + ivacaftor versus the ACT.

Due to a lack of directly comparative studies, the company carried out an additional information retrieval on other 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 transferring added benefit from the following patient groups to the target population of the present therapeutic indication:

- Patients from 6 to 11 years of age who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation on the 2nd allele (transfer of added benefit between different mutation types)
- Patients aged 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and have an RF mutation on the 2nd allele (transfer of added benefit between age groups)

The company's approach is unsuitable for drawing any conclusions on the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT. 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 regarding the transferability of study results from patients in the target population's age group but with different mutation types as well as from patients aged 12 years and older with the target population's mutation type. Both approaches are discussed in more detail below.

The company's arguments for the transferability of added benefit from different mutation types include results of the VX19-445-116 RCT [3], the VX18-445-106 single-arm study [4], and the associated extension study VX19-445-107 [5]. Referring to said studies, the company presents the results in Module 4 A and Module 4 B of the dossier. 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 assessment on Commission A22-15 and A22-21 [6].

In its discussion regarding the transferability of added benefit between different mutation types, 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 from 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 explains that favourable treatment effects have been proven for the combination of tezacaftor/ivacaftor + ivacaftor with the CFTR corrector elexacaftor in patients with heterozygous F508del mutation and an MF mutation on the 2nd allele. In the company's view, this demonstrates that the triple combination is more effective than the dual combination. The company concludes that, in patients with heterozygous F508del mutation and RF mutation on the 2nd allele, the intervention is more effective overall than the ACT. 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.

The company's reasoning regarding the transfer of added benefit between different age groups is based largely on results from the RCT VX18-445-104 from the previously assessed therapeutic indication with patients ages 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and have an RF mutation on the 2nd allele (see benefit assessments A21-72 [7] and A21-75 [8]). The company cites the results of this study, arguing that ivacaftor/tezacaftor/elexacaftor + ivacaftor is superior to tezacaftor/ivacaftor + ivacaftor for selected outcomes from the categories of morbidity, health-related quality of life, and side effects. In the company's opinion, the effectiveness of the triple combination in patients aged 12 years and older with an RF mutation on the 2nd allele has been proven by the results of the VX18-445-104 study.

No transferability of added benefit

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 the ACT, tezacaftor/ivacaftor + ivacaftor, for the therapeutic indication to be assessed. Regarding the transfer 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, it is impossible to transfer study results from patients with a different mutation type to the patient group in the present therapeutic indication on the basis of the information submitted by the company.

Furthermore, the company's reasoning regarding the transfer of added benefit between different mutation types is based, in part, on the results of the RCT VX19-445-116, which compared ivacaftor/tezacaftor/elexacaftor + ivacaftor versus placebo (plus BSC in both study arms). However, the G-BA specified a different ACT, the drug combination tezacaftor/ivacaftor + ivacaftor, for the present therapeutic indication. Consequently, the ACT differs for the 2 populations, and a key criterion for the transfer of results from the RCT VX19-445-116 to the population in the present therapeutic indication is not met.

The company's reasoning regarding the transfer of added benefit from patients aged 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and have an RF mutation on the 2nd allele to the younger target population in the therapeutic indication with the same mutation type is largely based on the VX18-445-104 study. However, this study was unsuitable for the benefit assessment in patients 12 years and older due to its short duration of 8 weeks (dossier assessments A21-72 and A21-75 [7,8]). For the mutation type in the present therapeutic indication, the added benefit was consequently rated as not proven for the age group 12 years and older [9,10]. Hence, irrespective of the transferability of results from patients aged 12 years and older to the age group in the present therapeutic indication, no relevant results are available for patients in either of the 2 age groups who are heterozygous for the F508del mutation and have an RF mutation on the 2nd allele.

Summary

Neither for the intervention nor for the ACT are data are available for the target population in the present therapeutic indication. Furthermore, regarding the transfer of added benefit between the 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 for the patients relevant in the present research question. In addition, the company bases its reasoning in part on results which are unsuitable for the benefit assessment and hence for transfer because of their differing ACT or short study duration. All in all, neither from patients with a different mutation type nor from older patients 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.

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 6 to 11 years who are heterozygous for the F508del mutation in the CFTR gene and have an RF mutation on the 2nd allele. 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 from 6 to 11 years of age who are heterozygous for the F508del mutation in the CFTR gene and have an RF mutation on the 2nd allele	Tezacaftor/ivacaftor in combination with ivacaftor	Added benefit not proven
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee; 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 transferred the added benefit established in patients in the same age group with heterozygous F508del mutation and an MF mutation on the 2nd allele as well as in patients 12 years and older with the same mutation type to the present therapeutic indication, claiming an indication of nonquantifiable added benefit.

The G-BA decides on the added benefit.

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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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