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Ivacaftor (combination with ivacaftor/ tezacaftor/elexacaftor; CF, 12 years and older, F508del, other/ unknown mut., heteroz.) –

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 (Kombination mit Ivacaftor/Tezacaftor/Elexacaftor; zystische Fibrose, ab 12 Jahre, F508del-Mutation, andere / unbekannte 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
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 ivacaftor in combination with 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 27 May 2021.

Research question

The aim of the present report is to assess the added benefit of ivacaftor in combination with ivacaftor/tezacaftor/elexacaftor (hereinafter referred to as ivacaftor + ivacaftor/tezacaftor/ elexacaftor) in comparison with best supportive care (BSC) as the appropriate comparator therapy (ACT) in cystic fibrosis (CF) patients 12 years and older who are heterozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene and have a mutation on the 2nd allele other than a minimal-function (MF), gating, or residual function (RF) mutation or in whom the mutation on the 2nd allele is unknown (also referred to as "other/unknown mutation").

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 + ivacaftor/tezacaftor/elexacaftor

Indication	**ACT[a]**
CF patients aged 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and have a mutation[b] other than an MF, gating, or RF mutation on the 2nd allele 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. 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 company additionally specified that best possible, individualized symptomatic therapy also represents the basic therapy for the drug to be assessed, ivacaftor + ivacaftor/tezacaftor/ elexacaftor. This 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.

Study pool

In agreement with the company's findings, the check for completeness of the study pool did not reveal any RCTs with ivacaftor + ivacaftor/tezacaftor/elexacaftor in the therapeutic indication to be assessed.

Despite this lack of evidence, the company derived an added benefit in the present therapeutic indication by extending the added benefit established for patients with an MF mutation on the 2nd allele to the target population. The company's approach is unsuitable for assessing the added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor.

Company's approach

The company did not identify any RCTs for assessing the added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor in the present therapeutic indication. Nevertheless, the company derived an added benefit by extending the added benefit established for patients with an MF mutation on the 2nd allele to the target population.

The company based its argument on results from the previously assessed therapeutic indication with patients aged 12 years and older who are heterozygous for the F508del mutation in the CTFR gene and have an MF mutation on the 2nd allele (see benefit assessment A20-83 and addendum A21-04). Said assessment derived a hint of major added benefit versus BSC on the basis of a 24-week RCT.

The company argues that the favourable clinical effect in patients with an MF mutation on the 2nd allele is based solely on the effect of therapy on the F508del mutation, while the MF allele does not contribute to effectiveness. The company bases this argument, firstly, on the broad approval of the triple combination for all patients who have at least 1 copy of the F508del mutation in the CFTR gene, regardless of the type of mutation on the 2nd allele. Secondly, the company cites comparable effectiveness, as measured by change in pulmonary function, between patients with different MF mutation subtypes (e.g., Class 1 or Class 2 MF mutations).

Overall, the company argues that patients in the present therapeutic indication possess, on the 1 allele with the F508del mutation, a mutation that is critical for the effectiveness of the triple combination, with the mutation on the 2nd allele exhibiting either no response or an additional response – as is the case in MF mutations. The company therefore expects the effectiveness in the present therapeutic indication to represent a mixed effect, but to be no less than in patients with an MF mutation on the 2nd allele.

Added benefit not transferable

For the therapeutic indication to be assessed, the dossier does not include studies with the intervention investigated in the present benefit assessment, nor does it contain any other information on the course of disease under BSC.

The company makes a purely qualitative argument through the intervention's principle of action rather than submitting any data on patient-relevant outcomes in the patients relevant for the present research question. On the basis of the information submitted by the company, it is therefore impossible to extend evidence from results in patients with an MF mutation on the 2nd allele to the present therapeutic indication, despite the fact that they share the same ACT.

Results on added benefit

No suitable data are available for assessing the added benefit of ivacaftor + ivacaftor/tezacaftor/ elexacaftor versus the ACT in CF patients aged 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and have, on the 2nd allele, either a mutation other than an MF, gating, or RF mutation or an unknown mutation. Consequently, there is no hint of an added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor 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]

On the basis of the results presented, the probability and extent of added benefit of the drug ivacaftor + ivacaftor/tezacaftor/elexacaftor in comparison with the ACT are assessed as follows:

Table 3 shows a summary of the probability and extent of added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor.

[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 + ivacaftor/tezacaftor/elexacaftor – 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 mutation[b] other than an MF, gating, or RF mutation on the 2nd allele 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.

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 G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is to assess the added benefit of ivacaftor in combination with ivacaftor/tezacaftor/elexacaftor (hereinafter referred to as ivacaftor + ivacaftor/tezacaftor/elexacaftor) in comparison with BSC as the ACT in CF patients 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and have a mutation on the 2nd allele other than an MF, gating, or RF mutation or in whom the mutation on the 2nd allele is unknown (also referred to as "other/unknown mutation").

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 + ivacaftor/tezacaftor/elexacaftor

Indication	**ACT**[a]
CF patients aged 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and have a mutation[b] other than an MF, gating, or RF mutation on the 2nd allele 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. 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 company additionally specified that best possible, individualized symptomatic therapy also represents the basic therapy for the drug to be assessed, ivacaftor + ivacaftor/tezacaftor/elexacaftor. This 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 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 cited by the company in the dossier:

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

- search on the G-BA website for ivacaftor + ivacaftor/tezacaftor/elexacaftor (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 May 2021); see Appendix A of the full dossier assessment for the search strategies.

In agreement with the company's findings, the check for completeness of the study pool did not reveal any RCTs with ivacaftor + ivacaftor/tezacaftor/elexacaftor in the therapeutic indication to be assessed. The company did not conduct any searches for further studies.

Despite this lack of evidence, the company derived an added benefit in the present therapeutic indication by extending the added benefit established for patients with an MF mutation on the 2nd allele to the target population. The company's approach is unsuitable for assessing the added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor. The reasoning is provided below.

Company's approach

The company based its argument on results from the previously assessed therapeutic indication of patients aged 12 years and older who are heterozygous for the F508del mutation in the CTFR gene and have an MF mutation on the 2nd allele (see dossier assessment A20-83 and Addendum A21-04 [3,4]). Said assessment derived a hint of major added benefit versus BSC on the basis of a 24-week RCT.

The company argues that the favourable clinical effect in patients with an MF mutation on the 2nd allele is based solely on the effect of therapy on the F508del mutation, while the MF allele does not contribute to effectiveness. The company bases this argument, firstly, on the broad approval of the triple combination for all patients who have at least 1 copy of the F508del mutation in the CFTR gene, regardless of the type of mutation on the 2nd allele. Secondly, the company cites comparable effectiveness, as measured by change in pulmonary function, between patients with different MF mutation subtypes (e.g., Class 1 or Class 2 MF mutations). The company asserts that no lower effectiveness is observed in Class 1 mutations, where no CFTR protein is formed at all, thus representing the worst case. It concludes that the response in the very heterogeneous mutations of the present therapeutic indication should exceed the response in MF mutations, which do not contribute to effectiveness at all. Further, the company cites in vitro data on a single component of the triple combination which were published on individual mutations (2nd allele) in the present therapeutic indication, showing, e.g., that ivacaftor improved function in the T338I, I336K, and E92K mutations (no MF, gating, or RF mutations) between 4-fold and 7-fold.

Overall, the company argues that patients in the present therapeutic indication possess, on the 1 allele with the F508del mutation, a mutation that is critical for the effectiveness of the triple

combination, with the mutation on the 2nd allele exhibiting no response or an additional response – as is the case in MF mutations. The company therefore expects the effectiveness in the present therapeutic indication to represent a mixed effect, but to be no less than in patients with an MF mutation on the 2nd allele.

Added benefit not transferable

For the therapeutic indication to be assessed, the dossier does not contain any studies, whether RCTs or 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. 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. The information submitted by the company therefore does not allow evidence to be extended from patients with an MF mutation on the 2nd allele to the present therapeutic indication despite the fact that they share the same ACT.

Further, the company did not conduct a current search on the therapeutic indication in patients with an MF mutation on the 2nd allele, but instead referred to the dossier from 26 August 2020. As a result, the data used by the company are potentially incomplete.

2.4 Results on added benefit

No suitable data are available for assessing the added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor versus the ACT in CF patients aged 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and have, on the 2nd allele, either a mutation other than an MF-, gating, or RF mutation or an unknown mutation. Consequently, there is no hint of an added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor 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 + ivacaftor/tezacaftor/elexacaftor in comparison with the ACT.

Table 5: Ivacaftor + ivacaftor/tezacaftor/elexacaftor – 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 mutation[b] other than an MF, gating, or RF mutation on the 2nd allele 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.

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 above assessment departs from that by the company, which extended the added benefit established in patients with an F508del and MF mutation to the present therapeutic indication and derived a hint of major 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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