



IQWiG Reports – Commission No. A20-108

**Tezacaftor/ivacaftor
(combination with ivacaftor;
cystic fibrosis, 6 to 11 years,
F508del mutation,
heterozygous) –**

**Benefit assessment according to §35a
Social Code Book V¹**

Extract

¹ Translation of Sections 2.1 to 2.5 of the dossier assessment *Tezacaftor/Ivacaftor (Kombination mit Ivacaftor; zystische Fibrose, 6 bis 11 Jahre, F508del-Mutation, heterozygot) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 25 February 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)
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 tezacaftor/ivacaftor 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 30 November 2020.

Research question

The aim of this report is to assess the added benefit of tezacaftor/ivacaftor plus ivacaftor in comparison with the appropriate comparator therapy (ACT) of best supportive care (BSC) in cystic fibrosis (CF) patients 6 to 11 years of age who are heterozygous for the F508del mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, or 3849+10kbC→T.

The ACT specified by the G-BA served as the basis for the research question presented in Table 2 of this benefit assessment.

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

Therapeutic indication	ACT ^a
CF patients 6 to 11 years of age who are heterozygous for the F508del mutation and have one of the following mutations in the CFTR gene ^b : P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T	BSC ^c
<p>a. Presented is the ACT specified by the G-BA. b. These are RF mutations. c. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.</p> <p>ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee; RF: residual function</p>	

The company designated BSC as the ACT, thus following the G-BA’s specification. The company also stated that the drug to be assessed, tezacaftor/ivacaftor + ivacaftor, was used in addition to individually optimized symptomatic therapy, and this was included in the presentation of added benefit.

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.

Results

For this therapeutic indication, the company identified no relevant RCT comparing tezacaftor/ivacaftor + ivacaftor with the ACT of BSC. Therefore, the company has submitted results from the single-arm study VX15-661-113. This study included CF patients 6 to 11 years of age who were either homozygous or heterozygous for the F508del mutation. The study consisted of 2 parts, with the treatment being administered for 14 days in the first part (Part A) and for 24 weeks in the second one (Part B). The company's dossier refers exclusively to the second part of the study.

The second part included 70 children, of which 9 (12.9%) were heterozygous for the F508del mutation.

Since it does not allow a comparison with the ACT, the single-arm VX15-661-113 study is unsuitable for deriving an added benefit of tezacaftor/ivacaftor + ivacaftor. The company has not submitted any data on the ACT.

Overall, the company's dossier does not present any suitable data for assessing the added benefit of tezacaftor/ivacaftor + ivacaftor in comparison with the ACT.

Probability and extent of added benefit, patient groups with therapeutically important added benefit³

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

Table 3 shows a summary of the probability and extent of added benefit of tezacaftor/ivacaftor + 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: Tezacaftor/ivacaftor + ivacaftor – probability and extent of added benefit

Indication	ACT ^a	Probability and extent of added benefit
CF patients 6 to 11 years of age who are heterozygous for the F508del mutation and have one of the following mutations in the CFTR gene ^b : P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T	BSC ^c	Added benefit not proven
<p>a. Presented is the ACT specified by the G-BA.</p> <p>b. These are RF mutations.</p> <p>c. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.</p> <p>ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee; RF: residual function</p>		

The G-BA decides on the added benefit.

2.2 Research question

The aim of this report is to assess the added benefit of tezacaftor/ivacaftor plus ivacaftor in comparison with the ACT of BSC in CF patients 6 to 11 years of age who are heterozygous for the F508del mutation and have one of the following mutations in the CFTR gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, or 3849+10kbC→T.

The ACT specified by the G-BA served as the basis for the research question presented in Table 4 of this benefit assessment.

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

Indication	ACT ^a
CF patients 6 to 11 years of age who are heterozygous for the F508del mutation and have one of the following mutations in the CFTR gene ^b : P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, or 3849+10kbC→T	BSC ^c
<p>a. Presented is the ACT specified by the G-BA. b. These are RF mutations. c. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.</p> <p>ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee; RF: residual function</p>	

The company designated BSC as the ACT, thus following the G-BA's specification. The company also stated that the drug to be assessed, tezacaftor/ivacaftor + ivacaftor, was used in addition to individually optimized symptomatic therapy, and this was included in the presentation of added benefit.

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 lists on tezacaftor/ivacaftor (status: 1 October 2020)
- bibliographic literature search on tezacaftor/ivacaftor (most recent search on 6 October 2020)
- search in trial registries / study results databases on tezacaftor/ivacaftor (most recent search on 1 October 2020)
- search on the G-BA website for tezacaftor/ivacaftor (most recent search on 1 October 2020)

To check the completeness of the study pool:

- search in trial registries on tezacaftor/ivacaftor (most recent search on 11 December 2020)

Concurring with the company, no relevant RCT on the direct comparison of tezacaftor/ivacaftor + ivacaftor versus the ACT was identified from the check.

Evidence provided by the company

During its information retrieval for further studies related to the intervention, the company identified the VX15-661-113 study [3], which it relied on to derive added benefit. The company has not conducted any information retrieval on the ACT.

VX15-661-113 is a single-arm study of tezacaftor/ivacaftor + ivacaftor. This study included CF patients 6 to 11 years of age who were either homozygous or heterozygous for the F508del mutation. The study consisted of 2 parts, with the treatment being administered for 14 days in the first part (Part A) and for 24 weeks in the second one (Part B). The company's dossier refers exclusively to the second part of the study.

The second part included a total of 70 children, of which 9 (12.9%) were heterozygous for the F508del mutation and hence relevant for the present research question.

In some of the children with the relevant mutation, treatment with tezacaftor/ivacaftor + ivacaftor departed from the specifications of the Summary of Product Characteristics. As approved, tezacaftor/ivacaftor + ivacaftor is administered to children with a body weight < 30 kg in the following dosage: fixed combination tablet of tezacaftor/ivacaftor (50 mg/75 mg) in the morning and 1 additional ivacaftor tablet (75 mg) in the evening. The dose is to be doubled for children with a body weight ≥ 30 kg [4]. In the VX15-661-113 study, children received the higher dose at a body weight ≥ 40 kg. Hence, the intervention was underdosed for children weighing ≥ 30 kg < 40 kg, affecting 3 of the 9 children (33.3%) in the study who were heterozygous for the F508del mutation.

Since it does not allow a comparison with the ACT, the single-arm VX15-661-113 study is unsuitable for deriving an added benefit of tezacaftor/ivacaftor + ivacaftor. The company has not submitted any data on the ACT.

Departing from this assessment, the company used the VX15-661-113 study to derive added benefit. The company deems individual results of the VX15-661-113 study to be confirmed by the results of the 8-week RCT VX16-661-115 [5] and the single-arm extension study VX17-661-116 [6]. Despite mentioning the two studies merely descriptively as part of the added-benefit discussion, the company does derive an added benefit based on the single-arm VX15-661-113 study. This notwithstanding, neither study is suitable for assessing added benefit: the 8-week RCT VX16-661-115 has an insufficient study duration, and the single-arm VX17-661-116 study does not lend itself to any comparison with the ACT. Overall, the

company derives a non-quantifiable added benefit for tezacaftor/ivacaftor + ivacaftor, without discussing probability. The company's approach is not appropriate.

2.4 Results on added benefit

In its dossier, the company does not present any suitable data for assessing the added benefit of tezacaftor/ivacaftor + ivacaftor in comparison with the ACT. Consequently, there is no hint of added benefit of tezacaftor/ivacaftor + ivacaftor in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

Table 5 shows a summary of the probability and extent of added benefit of tezacaftor/ivacaftor + ivacaftor.

Table 5: Tezacaftor/ivacaftor + ivacaftor – probability and extent of added benefit

Indication	ACT ^a	Probability and extent of added benefit
CF patients 6 to 11 years of age who are heterozygous for the F508del mutation and have one of the following mutations in the CFTR gene ^b : P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, or 3849+10kbC→T	BSC ^c	Added benefit not proven
<p>a. Presented is the ACT specified by the G-BA. b. These are RF mutations. c. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.</p> <p>ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee; RF: residual function</p>		

The above assessment deviates from that by the company, which derived a non-quantifiable 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/a20-108.html>.