



IQWiG Reports – Commission No. A20-109

**Ivacaftor  
(combination with tezacaftor/  
ivacaftor; cystic fibrosis,  
6 to 11 years, F508del  
mutation, homozygous) –  
Benefit assessment according to §35a  
Social Code Book V<sup>1</sup>**

**Extract**

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<sup>1</sup> Translation of Sections 2.1 to 2.5 of the dossier assessment *Ivacaftor (Kombination mit Tezacaftor/Ivacaftor; zystische Fibrose, 6 bis 11 Jahre, F508del-Mutation, homozygot) – 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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<sup>2</sup> Table numbers start with “2” as numbering follows that of the full dossier assessment.

**List of abbreviations**

<b>Abbreviation</b>	<b>Meaning</b>
ACT	appropriate comparator therapy
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 ivacaftor in combination with tezacaftor/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 ivacaftor in combination with tezacaftor/ivacaftor in comparison with the appropriate comparator therapy (ACT) of lumacaftor/ivacaftor in patients with cystic fibrosis (CF) aged 6 to 11 years who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

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 ivacaftor + tezacaftor/ivacaftor

Indication	ACT <sup>a</sup>
CF patients 6 to 11 years of age who are homozygous for the F508del mutation in the CFTR gene	Lumacaftor/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	

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

This benefit assessment was conducted using the ACT specified by the G-BA, lumacaftor/ivacaftor. Providing additional symptomatic treatment for the patient population is reasonable.

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 ivacaftor + tezacaftor/ivacaftor with the ACT of lumacaftor/ivacaftor. Therefore, the company has presented 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, which included 70 children, of which 61 (87%) were homozygous 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 ivacaftor + tezacaftor/ivacaftor. The company has not presented any data on the ACT.

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

### Probability and extent of added benefit, patient groups with therapeutically important added benefit<sup>3</sup>

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

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

Table 3: Ivacaftor + tezacaftor/ivacaftor – probability and extent of added benefit

Indication	ACT <sup>a</sup>	Probability and extent of added benefit
CF patients aged 6 to 11 years who are homozygous for the F508del mutation in the CFTR gene	Lumacaftor/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

The G-BA decides on the added benefit.

<sup>3</sup> 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 in combination with tezacaftor/ivacaftor in comparison with the ACT of lumacaftor/ivacaftor in CF patients aged 6 to 11 years who are homozygous for the F508del mutation in the CFTR gene.

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 ivacaftor + tezacaftor/ivacaftor

Indication	ACT <sup>a</sup>
CF patients aged 6 to 11 years who are homozygous for the F508del mutation in the CFTR gene	Lumacaftor/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	

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

This benefit assessment was conducted using the ACT specified by the G-BA, lumacaftor/ivacaftor. Providing additional symptomatic treatment for the patient population is reasonable.

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 + tezacaftor (as of 1 October 2020)
- Bibliographic literature search on ivacaftor (most recent search on 6 October 2020)
- Search in trial registries / study results databases on ivacaftor + tezacaftor (most recent search on 1 October 2020)
- Search on the G-BA website for ivacaftor + tezacaftor (most recent search on 1 October 2020)

To check the completeness of the study pool:

- Search in trial registries for ivacaftor + tezacaftor (most recent search on 11 December 2020)

Consistent with the company's results, this search showed no relevant RCT suitable for the direct comparison of ivacaftor + tezacaftor/ivacaftor versus the ACT.

### **Evidence provided by the company**

In 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 ivacaftor + tezacaftor/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.

A total of 70 children were included in the second part of the study. Of these, 61 (87%) children are homozygous for the F508del mutation and hence relevant for this present research question.

In some of the children with the relevant mutation, treatment with ivacaftor + tezacaftor/ivacaftor departed from the specifications of the Summary of Product Characteristics. As approved, ivacaftor + tezacaftor/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  $\geq$  30 kg. In the VX15-661-113 study, children received the higher dose at a body weight  $\geq$  40 kg. Hence, the intervention was underdosed for children weighing  $\geq$  30 kg < 40 kg, affecting 18 of the 61 children (29.5%) in the study who were homozygous 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 ivacaftor + tezacaftor/ivacaftor. The company has not presented 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 [4] and the single-arm extension study VX17-661-116 [5]. Despite mentioning the two studies merely descriptively as part of the added-benefit discussion of added benefit, 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 ivacaftor + tezacaftor/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 ivacaftor + tezacaftor/ivacaftor in comparison with the ACT. Consequently, there is no hint of added benefit of ivacaftor + tezacaftor/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 ivacaftor + tezacaftor/ivacaftor.

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

Indication	ACT <sup>a</sup>	Probability and extent of added benefit
CF patients aged 6 to 11 years who are homozygous for the F508del mutation in the CFTR gene	lumacaftor/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		

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.

1. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.0 [online]. 2020 [Accessed: 22.03.2021]. URL: [https://www.iqwig.de/methoden/general-methods\\_version-6-0.pdf](https://www.iqwig.de/methoden/general-methods_version-6-0.pdf).
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*The full report (German version) is published under <https://www.iqwig.de/en/projects/a20-109.html>.*