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Ivacaftor (combination with ivacaftor/ tezacaftor/elexacaftor; cystic fibrosis, 12 years and older, F508del mut., homozygous) –

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, homozygot) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 November 2020). 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.

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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
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
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)
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 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 1 September 2020.

Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

Research question

The aim of the present report is the assessment of the added benefit of ivacaftor in combination with ivacaftor/tezacaftor/elexacaftor (hereinafter referred to as "ivacaftor + ivacaftor/tezacaftor/elexacaftor") in comparison with the appropriate comparator therapy (ACT) in patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

For the present benefit assessment, the GB-A's specification of the ACT resulted in the research question presented in Table 2.

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

Therapeutic indication	**ACT[a]**
CF patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene	Lumacaftor/ivacaftor or **tezacaftor/ivacaftor in combination with ivacaftor**
a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. ACT: appropriate comparator therapy; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee	

The company chose tezacaftor/ivacaftor in combination with ivacaftor (hereinafter referred to as "ivacaftor + tezacaftor/ivacaftor") from the options presented above and thus followed the G-BA's specification of the ACT. The company stated that the ACT ivacaftor + tezacaftor/ ivacaftor, like ivacaftor + ivacaftor/tezacaftor/elexacaftor, the drug to be assessed, was used in addition to an individual best symptomatic treatment, which was included in the presentation of the added benefit.

The present benefit assessment was conducted in comparison with the ACT specified by the G-BA. An additional symptomatic treatment for the patient population is comprehensible.

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 the added benefit.

Results

Evidence provided by the company

In its dossier, the company used the VX17-445-103 study for the assessment of the added benefit. Study VX17-445-103 is a randomized, double-blind phase 3 study comparing 4 weeks of treatment with ivacaftor + ivacaftor/tezacaftor/elexacaftor versus ivacaftor + ivacaftor/ tezacaftor. The patients in the study correspond to the therapeutic indication relevant to the present benefit assessment.

Due to the study duration of only 4 weeks, the VX17-445-103 study included by the company is unsuitable for a benefit assessment in the therapeutic indication of CF. CF is a chronic disease requiring lifelong treatment. No conclusions can be drawn on the basis of short-term studies as to whether short-term effects persist in the longer term. It is also not possible to record any effects that only become apparent in the longer term, such as for pulmonary exacerbations and their consequences or for adverse events. The company justified the inclusion criterion of 4 weeks used by the company with the explanation that this was the maximum treatment duration in the only randomized approval study and the basis of the approval decision. The company's rationale was not followed.

Overall, studies of at least 24 weeks are necessary to compare benefit and harm for the benefit assessment in the therapeutic indication of CF. Hence, the VX17-445-103 study was too short to be included in the present benefit assessment.

Study VX18-445-109 announced by the company

The company also stated that it would submit results from the recently completed study VX18-445-109. The study is potentially relevant for the assessment of the added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor in comparison with the ACT. However, no results of this study have become available yet.

Results on added benefit

No suitable data are available for the assessment of the added benefit of ivacaftor + ivacaftor/ tezacaftor/elexacaftor in comparison with the ACT in patients with CF aged 12 years and older who are homozygous for the F508del mutation. Hence, 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 the added benefit of the drug ivacaftor + ivacaftor/tezacaftor/elexacaftor compared with the ACT is assessed as follows:

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

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

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
CF patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene	Lumacaftor/ivacaftor or **tezacaftor/ivacaftor in combination with ivacaftor**	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.

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.

[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].

2.2 Research question

The aim of the present report is the assessment of the added benefit of ivacaftor + ivacaftor/ tezacaftor/elexacaftor in comparison with the ACT in patients with CF aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene.

For the present benefit assessment, the GB-A's specification of the ACT resulted in the research question presented in Table 4.

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

Therapeutic indication	**ACT**[a]
CF patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene	Lumacaftor/ivacaftor or **tezacaftor/ivacaftor in combination with ivacaftor**
a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. ACT: appropriate comparator therapy; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee	

The company chose ivacaftor + tezacaftor/ivacaftor from the options presented above and thus followed the G-BA's specification of the ACT. The company stated that the ACT ivacaftor + tezacaftor/ivacaftor, like ivacaftor + ivacaftor/tezacaftor/elexacaftor, the drug to be assessed, was used in addition to an individual best symptomatic treatment, which was included in the presentation of the added benefit.

The present benefit assessment was conducted in comparison with the ACT specified by the G-BA. An additional symptomatic treatment for the patient population is comprehensible.

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 the added benefit. This deviates from the company's inclusion criteria, which specified a minimum duration of 4 weeks.

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 + ivacaftor/tezacaftor/elexacaftor (status: 9 July 2020)
- bibliographical literature search on ivacaftor + ivacaftor/tezacaftor/elexacaftor (last search on 9 July 2020)
- search in trial registries/trial results databases for studies on ivacaftor + ivacaftor/tezacaftor/elexacaftor (last search on 9 July 2020)
- search on the G-BA website for ivacaftor + ivacaftor/tezacaftor/elexacaftor (last search on 9 July 2020)

To check the completeness of the study pool:

- search in trial registries for studies on ivacaftor + ivacaftor/tezacaftor/elexacaftor (last search on 8 September 2020)

The check identified the VX18-445-109 study [3] as a potentially relevant study. According to the information provided in Module 4 B, this study had just been completed, and the company stated that it would submit the data of this study later (see below for information on the study). Besides this, the check did not identify any potentially relevant studies.

Evidence provided by the company

In its dossier, the company used the VX17-445-103 study [4] for the assessment of the added benefit. Study VX17-445-103 is a randomized, double-blind phase 3 study comparing 4 weeks of treatment with ivacaftor + ivacaftor/tezacaftor/elexacaftor versus ivacaftor + ivacaftor/ tezacaftor. The patients in the study correspond to the therapeutic indication relevant to the present benefit assessment. In Module 4 B, the company justified the inclusion criterion regarding the study duration of 4 weeks used by the company with the explanation that this was the maximum treatment duration in the only randomized approval study and the basis of the approval decision.

Due to the treatment phase of only 4 weeks, the VX17-445-103 study included by the company is unsuitable for a benefit assessment in the therapeutic indication of CF. CF is a chronic disease requiring lifelong treatment. The European Medicines Agency (EMA) guideline recommends a minimum duration of 6 months for the investigation of a clinical outcome [5]. IQWiG's *General Methods* also consider long-term studies to be necessary for the benefit assessment in chronic diseases [1]. Short-term studies are inadequate for the benefit assessment in the therapeutic indication of CF, as ivacaftor is a long-term treatment. No conclusions can be drawn on the basis of short-term studies as to whether short-term effects persist in the longer term. It is also not possible to record any effects that only become apparent in the longer term, such as

for pulmonary exacerbations and their consequences or for adverse events. Pulmonary exacerbations are a common cause of lung damage or death in patients with CF [6-9]. Besides, the company itself set up a study with a 24-week treatment phase (VX18-445-109). It was therefore assumed that the company also considered a longer study duration to be reasonable.

Overall, studies of at least 24 weeks are necessary to compare benefit and harm for the benefit assessment in the therapeutic indication of CF. Hence, the VX17-445-103 study was too short to be included in the present benefit assessment. Thus, deviating from the company, this study was not used for the benefit assessment of ivacaftor in the present therapeutic indication.

In its dossier (Module 4 B, Section 4.3.2.3), the company additionally presented results from the single-arm study VX17-445-105 [10] (after 24 and 36 weeks). This study is an extension study in which, among others, patients from the VX17-445-103 study continued to receive treatment with ivacaftor + ivacaftor/tezacaftor/elexacaftor. These results are not relevant for the present benefit assessment, as there are no data for an assessment of ivacaftor + ivacaftor/ tezacaftor/elexacaftor in comparison with the ACT.

Study VX18-445-109 announced by the company

The recently completed double-blind RCT VX18-445-109 compared ivacaftor + ivacaftor/ tezacaftor/elexacaftor with ivacaftor + ivacaftor/tezacaftor in patients with CF aged 12 years and older who are homozygous for the F508del mutation. A total of 176 patients were included and treated for 24 weeks. According to the registry entry, the study recorded outcomes in the categories of morbidity and side effects.

Overall, the VX18-445-109 study is potentially relevant for the assessment of the added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor in comparison with the ACT. However, no results of this study have become available yet. According to the company, the results of the study will be submitted later.

2.4 Results on added benefit

No suitable data are available for the assessment of the added benefit of ivacaftor + ivacaftor/ tezacaftor/elexacaftor in comparison with the ACT in patients with CF aged 12 years and older who are homozygous for the F508del mutation. Hence, 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

The result of the assessment of the added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor in comparison with the ACT is summarized in Table 5.

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

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
CF patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene	Lumacaftor/ivacaftor or **tezacaftor/ivacaftor in combination with ivacaftor**	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.

ACT: appropriate comparator therapy; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee

The assessment described above deviates from that of the company, which derived an indication 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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The full report (German version) is published under https://www.iqwig.de/en/projects/a20-77.html.