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Ivacaftor (cystic fibrosis, 4 to < 6 months, with gating mutations) –

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 (zystische Fibrose, 4 bis < 6 Monate, mit Gating-Mutationen) – 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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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
BSC	best supportive care
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
FEV1	forced expiratory volume in 1 second
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LCI	lung clearance index
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. 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 November 2020.

Research question

The aim of this report is to assess the added benefit of ivacaftor in comparison with best supportive care (BSC) as the appropriate comparator therapy (ACT) in cystic fibrosis (CF) patients 4 to < 6 months of age with a body weight of at least 5 kg who have one of the following gating mutations (class III) in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R.

Table 2: Research question of the benefit assessment of ivacaftor

Indication	ACT[a]
CF patients 4 to < 6 months of age with a body weight of at least 5 kg who have one of the following gating mutations (class III) in the CFTR gene: G551D, G551S, G1244E, G1349D, G178R, S1251N, S1255P, S549N, or S549R	BSC[b]

a. Presented is the ACT specified by the G-BA.
b. 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.

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

The company designated BSC 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

For this therapeutic indication, the company identified no relevant RCT comparing ivacaftor with the ACT of BSC. Therefore, the company has presented results from the single-arm study VX15-770-124, which included CF patients 4 to < 6 months of age with of the following CFTR gating mutations in at least 1 allele: G551D, G551S, G1244E, G1349D, G178R, S1251N, S1255P, S549N, or S549R. The study consisted of 2 parts (Parts A and B), with Part B having a duration of 24 weeks. The latter is the part analysed in the benefit assessment. The company did not look for data on the ACT. Since VX15-770-124 is merely a single-arm study, the company additionally included 3 RCTs on older patients (6 years or above). In the company's

view, these data can be extrapolated to children 4 to < 6 months of age and are suitable for deriving added benefit. The company reasons that it deems the intervention's mechanism of action, the disorder's clinical picture as well as the efficacy and safety of ivacaftor to be sufficiently comparable for children 4 to < 6 months of age and patients 6 years and older. It concludes that the evidence available for patients 6 years and older can be used to derive added benefit for children 4 to < 6 months of age. The studies VX12-770-111, VX08-770-102, and VX08-770-103 on patients 6 years and older are the subject of the prior dossier assessments A19-65 and A19-66.

Added benefit not extrapolatable

Given the lack of direct comparative data for children 4 to < 6 months of age, the company's intention of extrapolating study results from older patients to the population relevant for the benefit assessment is understandable. However, the company's specific implementation of this extrapolation is unsuitable. For the following reasons, the data presented by the company cannot be used to derive an added benefit of ivacaftor in comparison with the ACT for children 4 to < 6 months of age:

Studies VX12-770-111, VX08-770-102, and VX08-770-103

VX12-770-111 is a randomized cross-over study with a treatment duration of 8 weeks. It included patients 6 years and older with the following gating mutations: G551S, G1244E, G1349D, G178R, S1251N, S1255P, S549N, S549R, or G970R. The treatment duration of 8 weeks is too short for a benefit assessment in the therapeutic indication of CF.

VX08-770-102 and VX08-770-103 are RCTs with a treatment duration of 48 weeks. These studies included patients with the gating mutation G551D who were 12 years and older (VX08-770-102) or 6 to 11 years of age (VX08-770-103). Extrapolating data from these two studies to children from 4 to < 6 months of age is inappropriate for the following reasons:

- Different effects of ivacaftor versus BSC depending on disease stage
  - CF is a progressive disorder. Therefore, the extrapolatability of results becomes the more questionable the greater the age gap between the population to be studied and the population from which the data are to be extrapolated. The data presented on the 2 studies VX08-770-102 and VX08-770-103 show differences in demographic and clinical characteristics between the populations included. In addition, the effects of ivacaftor versus the ACT of BSC differed in patient-relevant outcomes. Based on the data presented, it is assumed that, due to the progressive course of CF and the large age difference between the study populations, the children in the VX08-770-103 study were in a less advanced stage of disease than the patients in the VX08-770-102 study. For this reason, there is no meaningful way to extrapolate results from the VX08-770-102 study population to much younger children. This argument has already been made against the extrapolation of effects to children 12 to < 24 months of age in benefit assessment A19-69 and to slightly younger children 6 to < 12 months in

benefit assessment A19-105. However, the patient population for this benefit assessment, children 4 to < 6 months, is even younger than the patient populations of dossier assessments A19-69 and A19-105. In this benefit assessment, the age difference to the patient population of children 6 years and older, which the company uses to extrapolate added benefit, is therefore even greater.

- Lack of data for assessing the comparability of the outcomes of VX15-770-124 versus VX15-770-103

  For the following important parameters, it was impossible to assess comparability due to a lack of data:

  - For pulmonary exacerbation, a central patient-relevant outcome in the therapeutic indication of CF, the studies used by the company were based on different operationalizations. No data work-up is available regarding comparable operationalizations of this outcome in studies VX15-770-124 and VX15-770-103. Therefore, it is inappropriate to extrapolate the results from VX08-770-103 to children 4 to < 6 months.
  - With regard to lung function parameters, no data suitable for a comparison are available for the different age groups. Forced expiratory volume in 1 second (FEV1) was not surveyed in VX15-770-124, and for the lung clearance index (LCI), no data are available for Cohort 7 (VX08-770-103: LCI surveyed in 2 out of 38 children of the relevant subpopulation).

Irrespective of whether the results from VX08-770-103 are extrapolatable to children 4 to < 6 months, the study's outcomes included for benefit assessment A19-65 show neither effects in favour nor effects to the disadvantage of ivacaftor + BSC in comparison with BSC.

- Missing data on the ACT of BSC
  - The company has presented no data from studies with the ACT of BSC for children 4 to < 6 months of age, and consequently, the treatment effects of ivacaftor versus BSC cannot be assessed.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the presented results, the probability and extent of added benefit of the drug ivacaftor in comparison with the ACT have been assessed as follows:

Table 3 presents a summary of the results regarding the benefit assessment of ivacaftor in comparison with the ACT.

Table 3: Ivacaftor – probability and extent of added benefit

Indication	**ACT[a]**	**Probability and extent of added benefit**
CF patients 4 to < 6 months of age with a body weight of at least 5 kg who have one of the following gating mutations (class III) in the CFTR gene: G551D, G551S, G1244E, G1349D, G178R, S1251N, S1255P, S549N, or S549R	BSC[b]	Added benefit not proven
a. Presented is the ACT specified by the G-BA. b. 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. ACT: appropriate comparator therapy; BSC: best supportive care; 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 this report is to assess the added benefit of ivacaftor in comparison with BSC as the ACT in CF patients 4 to < 6 months of age with a body weight of at least 5 kg who have one of the following gating mutations (class III) in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R.

Table 4: Research question of the benefit assessment of ivacaftor

Indication	**ACT**[a]
CF patients 4 to < 6 months of age with a body weight of at least 5 kg who have one of the following gating mutations (class III) in the CFTR gene: G551D, G551S, G1244E, G1349D, G178R, S1251N, S1255P, S549N, or S549R	BSC[b]
a. Presented is the ACT specified by the G-BA. b. 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. ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee	

The company designated BSC 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 submitted by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of added benefit. This deviates from the company's inclusion criteria, which specified a minimum duration of 8 weeks.

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 (as of 21 September 2020)
- Bibliographic literature search on ivacaftor (most recent search on 22 September 2020)
- Search in trial registries / study results databases on ivacaftor (most recent search on 22 September 2020)
- Search on the G-BA website on ivacaftor (most recent search on 2 October 2020)

To check the completeness of the study pool:

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

Consistent with the company, the check of completeness of the study pool revealed no study for the direct comparison of ivacaftor with the ACT of BSC in this therapeutic indication.

The company's approach

To derive added benefit, the company has submitted results from the single-arm study VX15-770-124 [3,4] on children 4 to < 6 months of age. The company did not look for data regarding the ACT. Since VX15-770-124 is merely a single-arm study, the company also refers to G-BA assessments of 3 RCTs on older patients (6 years and older). In the company's view, these G-BA assessments can be extrapolated to children 4 to < 6 months of age and are suitable for deriving added benefit. For justification, the company claims sufficient comparability between children 6 to < 12 months of age and patients 6 years and older with respect to the intervention's mechanism of action, the disorder's clinical picture as well as the efficacy and safety of ivacaftor. However, the company fails to present a work-up of these data, which it deems relevant for the extrapolation of results. Hence, the data situation is comparable to the situation in dossier assessments A19-69 [5] (company dossier, Module 4 E [6]) and A19-105 [7] (company dossier, Module 4 F [8]), both of which pertain to slightly older children (12 to < 24 months and 6 to < 12 months) for the same therapeutic indication. For these assessments, the company likewise submitted data from the single-arm study VX15-770-124 with the results for the older patient cohorts and postulated that data from older children 6 years and older can be extrapolated.

Given the lack of direct comparative data for children 4 to < 6 months of age, the company's intention of extrapolating study results from older patients to the population relevant to this benefit assessment is understandable. However, as discussed in dossier assessments A19-69 [5] and A19-105 [7], the specific implementation of this extrapolation is inadequate. The data presented by the company are unsuitable for deriving an added benefit of ivacaftor in comparison with the ACT for children 4 to < 6 months of age. The reasoning is provided below.

Single-arm study with ivacaftor (VX15-770-124)

VX15-770-124 is a single-arm, open-label study with ivacaftor; it included CF patients 0 to < 24 months of age who had one of the following CFTR gating mutations in at least 1 allele: G551D, G551S, G1244E, G1349D, G178R, S1251N, S1255P, S549N, or S549R. The study was carried out in 2 parts or time periods (Parts A and B). Children in Part A were allocated by age to 1 of 4 cohorts, and those in Part B, in 1 of 3 cohorts. In both Part A and Part B of the study, ivacaftor granules were dosed according to body weight as specified in the Summary of Product Characteristics. Both parts of the study differed in terms of the investigated outcomes as well as treatment duration. Treatment was administered for 4 days in Part A and for 24 weeks in Part B. With respect to the benefit assessment and in light of the treatment duration, the company ignored this study phase of Part A and instead focused exclusively on Part B. Cohort 7 of this part of the study included children aged 4 to < 6 months. In the study, ivacaftor treatment was administered in addition to the concomitant CF therapy. Cohort 7 of the study consisted of 6 children. The children included in the VX15-770-124 study had the gating mutation G551D; in addition, 1 infant with R117 mutation was included. Further information on the characterization of the study and the intervention are found in dossier assessments A19-69 [5] and A19-105 [7]. The patient characteristics of the 6 children of Cohort 7 are found in Appendix A of the full dossier assessment.

Added benefit cannot be extrapolated from older populations

In its reasoning on the added benefit of ivacaftor for this therapeutic indication, the company relies on results from the studies VX12-770-111, VX08-770-102 and VX08-770-103 with patients 6 years and older. The company views it as self-evident that the results from these 3 studies can be extrapolated to the target population of children 4 to < 6 months of age. It aims to extrapolate the added benefit found in older patients to children with the same mutation aged 4 to < 6 months. The data from VX12-770-111, VX08-770-102, and VX08-770-103 are available in the dossier dated 29 August 2019 pertaining to the previous procedure for ivacaftor. In Module 4 B [9] of that dossier, the company presented the VX12-770-111 study, and in Module 4 A [10], the studies VX08-770-102 and VX08-770-103. In this regard, please also see dossier assessments A19-66 [11] and A19-65 [12].

Studies VX12-770-111, VX08-770-102, and VX08-770-103

VX12-770-111 is a randomized cross-over study with a treatment duration of 8 weeks. The study included patients 6 years and older with the following gating mutations: G551S, G1244E, G1349D, G178R, S1251N, S1255P, S549N, S549R, or G970R. At a treatment duration of 8 weeks, however, it is too short to be included in the benefit assessment for the therapeutic indication of CF. Detailed information on this study is found in dossier assessment A19-66 [11].

VX08-770-102 and VX08-770-103 are RCTs with a treatment duration of 48 weeks. These studies included patients with the gating mutation G551D who were 12 years and older (VX08-770-102) or 6 to 11 years of age (VX08-770-103). These two studies were the subject of dossier assessment A19-65 [12], which provides detailed information on the characterization of the studies, interventions, and included patients.

As described above, the company argues that the results of older patients can be extrapolated to the target population because it deems the intervention's mechanism of action, the disorder's clinical picture as well as efficacy and safety to be comparable. The company's approach for extrapolating results is inappropriate. This is particularly due to the following issues:

- Different effects of ivacaftor versus BSC depending on disease stage
  - CF is a progressive disorder. Therefore, the extrapolatability of results becomes the more questionable the greater the age gap between the population to be studied and the population from which the data are to be extrapolated. The analysis of the results from VX08-770-102 (patients 12 years and older) and VX08-770-103 (children 6 to 11 years) revealed differences in demographic and clinical characteristics of the included populations; these differences are largely the consequence of differences in the studies' inclusion and exclusion criteria. Due to the different populations and concurring with the company, no metaanalytical summary of results of the two above studies was conducted in benefit assessment A19-65. In addition, ivacaftor and the ACT of BSC differed in effects regarding patient-relevant outcomes (see dossier assessment A19-65). Based on the data presented, it is assumed that due to the

progressive course of CF and the large age difference between the study populations, the children in the VX08-770-103 study were in a less advanced stage of disease than the patients in the VX08-770-102 study. For this reason, there is no meaningful way to extrapolate results from the VX08-770-102 study population to much younger children. This argument has already been made against the extrapolation of effects to children 12 to < 24 months of age in benefit assessment A19-69 and to slightly younger children 6 to < 12 months in benefit assessment A19-105. The patient population of interest for this benefit assessment, children 4 to < 6 months, is even younger than the patient populations of dossier assessments A19-69 and A19-105. In this benefit assessment, the age difference to the patient population of children 6 years and older, which the company uses to extrapolate added benefit, is therefore even greater.

- Lack of data for assessing the comparability of the outcomes of VX15-770-124 versus VX15-770-103

  Appendix B of the full dossier assessment presents the results from the VX15-770-124 study for children 4 to < 6 months and from VX15-770-103 for children 6 to 11 years of age.

  For the following important parameters, it was impossible to assess comparability due to a lack of data:

  - A central patient-relevant outcome in the therapeutic indication of CF, pulmonary exacerbation, was based on different operationalizations in VX15-770-124 versus VX11-770-103. The studies differ both in the symptoms included in the operationalizations and in the persistence of symptoms. Table 10 in Appendix B of the full dossier assessment provides an overview of the operationalizations used in the studies. For this outcome, the company supplies no data work-up in terms of comparable operationalizations in the two studies. The VX15-770-124 study used 2 different operationalizations, leading to very different results even within this study. In addition, the results from VX15-770-124 markedly differ from those of VX15-770-103 with regard to both examined operationalizations. Therefore, it is impossible to ascertain the source of the differences in results between the studies with regard to this outcome. As a result, it is inappropriate to extrapolate the results from VX08-770-103 to children 4 to < 6 months. With regard to lung function parameters, no data suitable for a comparison are available for the different age groups. FEV1 was not surveyed in VX15-770-124, and for the LCI, no data are available for Cohort 7 (VX08-770-103: LCI surveyed in 2 out of 38 children of the relevant subpopulation).

- Missing data on the ACT of BSC

  - For children 4 to < 6 months of age, the company has presented no data from studies with the ACT of BSC; consequently, the treatment effects of ivacaftor in comparison

with BSC cannot be assessed. In the dossier, the company does not discuss the reasons why it conducted no information retrieval on the ACT.

Summary

In summary, the company's implementation of the extrapolation of the presented study results from patients 6 years and older to the target population is not suitable for deriving added benefit. Different effects were found already when comparing patients 12 years and older in VX08-770-102 versus children 6 to 11 years of age in VX08-770-103; therefore, extrapolating results to even younger children 4 to < 6 months of age is deemed inappropriate. Due to a lack of available data, it is impossible to properly evaluate the extrapolatability of evidence from VX08-770-103 participants 6 to 11 years of age. Irrespective of whether the results are extrapolatable, on the basis of the outcomes relevant for the benefit assessment, the VX08-770-103 study shows neither effects in favour nor effects to the disadvantage of ivacaftor + BSC in comparison with BSC (see dossier assessment A19-65 [12])

2.4 Results on added benefit

No suitable data are available for assessing the added benefit of ivacaftor in comparison with the ACT in CF patients 4 to < 6 months of age who have a gating mutation. Consequently, there is no hint of an added benefit of ivacaftor 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 regarding the benefit assessment of ivacaftor in comparison with the ACT.

Table 5: Ivacaftor – probability and extent of added benefit

Indication	**ACT**[a]	**Probability and extent of added benefit**
CF patients 4 to < 6 months of age with a body weight of at least 5 kg who have one of the following gating mutations (class III) in the CFTR gene: G551D, G551S, G1244E, G1349D, G178R, S1251N, S1255P, S549N, or S549R	BSC[b]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. 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.

BSC: best supportive care; 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.

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Please see full dossier assessment for full reference list.

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