IQWiG Reports – Commission No. A20-99

Ivacaftor (cystic fibrosis, 4 to < 6 months, with R117H mutation) –

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 R117H-Mutation) – 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.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Ivacaftor (cystic fibrosis, 4 to < 6 months, with R117H mutation) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
27 November 2020

Internal Commission No.
A20-99

Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- T.O.F. Wagner

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.

IQWiG employees involved in the dossier assessment

- Daniela Preukschat
- Katharina Biester
- Gertrud Egger
- Ulrich Grouven
- Marco Knelangen
- Ana Liberman
- Min Ripoll

Keywords: Ivacaftor, Cystic Fibrosis, Infant, Benefit Assessment

Table of contents

List of tables[2]

Page

[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
CFQ-R	Cystic Fibrosis Questionnaire – Revised
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)
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 an R117H mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

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

Indication	ACT[a]
CF patients 4 to < 6 months of age with a body weight of at least 5 kg who have an R117H mutation in the CFTR gene	BSC[b]

a. Presentation of the ACT specified by the G-BA.
b. 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

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 presents results from the single-arm VX15-770-124 study which included CF patients 4 to < 6 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 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 regarding the ACT. In addition, the company's

rationale regarding the added benefit of ivacaftor in this therapeutic indication is based on the results of the adult participants of the RCT VX11-770-110. 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. For justification, the company claims sufficient comparability between children 4 to < 6 months of age and adult patients 18 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. The company concludes that the evidence available for adults is suitable for deriving added benefit in children 4 to < 6 months of age. The VX11-770-110 study has already been evaluated in dossier assessments A19-68 and A20-52.

Added benefit cannot be extrapolated from adults

Given the lack of direct comparative data for children 4 to < 6 months of age, the company's intention of extrapolating study results from adults to the population relevant to the benefit assessment is understandable. However, the specific manner in which the extrapolation was implemented is equally as inappropriate in this assessment as it was in dossier assessment A20-52. 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.

VX11-770-110 is a randomized, double-blind study with a treatment duration of 24 weeks, comparing ivacaftor + BSC with placebo + BSC. It included CF patients ≥ 6 years of age with an R117H mutation in at least 1 allele of the CFTR gene. In terms of the extrapolation of added benefit, the company looks at the results of the adults in this study.

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.

As expected in a progressive disorder, the comparison of the VX11-770-110 results for adults versus patients from 6 to < 18 years of age reveals differences in both the clinical characteristics of the populations (e.g. forced expiratory volume in 1 second [FEV1] or *Pseudomonas aeruginosa* infection) and in the results, e.g. in the respiratory symptoms domain of the Cystic Fibrosis Questionnaire – Revised [CFQ-R] or the FEV1, which is presented as a supplementary outcome (also see benefit assessment A20-52). Overall, on the basis of the presented data and the progressive course of CF as well as the large difference in age, extrapolation of the results from adults to patients 6 to < 18 years of age or to patients 6 months to < 6 years of age was deemed inappropriate in assessment A20-52. Thus, extrapolating the results from adults to children who are even younger, aged 4 to < 6 months, is inappropriate as well.

In addition, the company presents no data from studies with the ACT of BSC for children 4 to < 6 months of age, and 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.

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 an R117H mutation in the CFTR gene	BSC[b]	Added benefit not proven

a. Presentation of the ACT specified by the G-BA.
b. 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

The G-BA decides on the added benefit.

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 an R117H mutation in the CFTR gene.

The G-BA's specification of the ACT results in the research question presented in Table 4.

[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 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 an R117H mutation in the CFTR gene	BSC[b]
a. Presented is the ACT specified by the G-BA. b. 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	

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. 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 (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.

Company's approach

To derive added benefit, the company presents results from the single-arm VX15-770-124 study [3,4] on children 4 to < 6 months of age. The company did not look for data on the ACT. In Module 4 H, the company also states that the evidence on added benefit is additionally based on the results of the RCT VX11-770-110 on ivacaftor in adult CF patients with R117H mutation (a study previously evaluated in dossier assessments A19-68 [5] and A20-52 [6]). 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. For justification, the company claims sufficient comparability between children 4 to < 6 months of age and adult patients 18 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 that found in dossier assessment A20-52 [6] (company's dossier, Module 4 G [7]) on the subject of older children (6 months to < 18 years) in the same therapeutic indication. For that assessment, the company likewise postulated extrapolatability of the data of the adults (≥ 18 years) in RCT VX11-770-110.

Given the lack of direct comparative data for children 4 to < 6 months of age, the company's intention of extrapolating study results from adults to the population relevant to this benefit assessment is understandable. However, as discussed in dossier assessment A20-52 [6], the specific implementation of the 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)

The VX15-770-124 study is a single-arm, open-label study with ivacaftor; the study was to include 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 included 6 children, but only 1 of them had an R117H mutation. The other 5 children exhibited the G551D gating mutation. Further information on the characterization of the study and the intervention are found in dossier assessments A19-69 [8] and A19-105 [9]. The company does not present separate results for the 1 child with R117H mutation; the results of Cohort 7 (n = 6) are found in dossier assessment A20-100 [10].

Added benefit not extrapolatable from adults

The company's reasoning regarding the added benefit of ivacaftor in this therapeutic indication relies on the results of the VX11-770-110 RCT. The company views it as self-evident that the results of adults in this study can be extrapolated to the target population of children 4 to < 6 months of age. It aims to extrapolate the added benefit found in adults to children with the same mutation aged 4 to < 6 months. The data of the VX11-770-110 study are available in the

dossier dated 29 August 2019 pertaining to the previous procedure for ivacaftor. Its Module 4 D, for instance, presents the results of adult participants of the VX11-770-110 RCT [11]. In this regard, please also see dossier assessment A19-68 [5]. In the current dossier, the company does not discuss the results of children in the VX11-770-110 study. The assessment of the results of the VX11-770-110 study for children aged 6 to < 18 years is found in the dossier assessment for commission A20-52 [6] (dossier of the company, Module 4 G [7]).

Study VX11-770-110

VX11-770-110 is a randomized, double-blind study with a treatment duration of 24 weeks, comparing ivacaftor + BSC with placebo + BSC. It included CF patients ≥ 6 years of age with an R117H mutation in at least 1 allele of the CFTR gene. This study was the subject of the dossier assessments for commissions A19-68 (adults) [5] and A20-52 (children, 6 months to < 18 years) [6]. As described above, the company aims to extrapoalte added benefit from this study on the basis of the results of adults. Detailed information on the characterization of the studies, interventions, and included patients are found in dossier assessments A19-68 and A20-52.

As described above, the company argues that the results of adults can be extrapolated to the target population because it deems the intervention's mechanism of action, the disorder's clinical picture, and efficacy and safety to be comparable. The company's approach for extrapolating results is inappropriate. The reasons are explained below.

CF is a progressive disorder. Therefore, the extrapolatabililty 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.

As expected in a progressive disorder, the comparison of the results from the VX11-770-110 RCT for adults versus patients from 6 to < 18 years of age reveals differences in the clinical characteristics of the populations (e.g. in FEV1 or *Pseudomonas aeruginosa* infection) as well as in the results, e.g. in the respiratory symptoms domain of the CFQ-R or the supplementary outcome of FEV1 (also see benefit assessment A20-52) [6]). Overall, on the basis of the presented data and the progressive course of CF as well as the large difference in age, extrapolating the results from adults to patients 6 to < 18 years of age or to patients 6 months to < 6 years of age was deemed inappropriate in assessment A20-52. Hence, it is equally as inappropriate to extrapolate the results of the adults to even younger children 4 to < 6 months in age.

In addition, the company presents no data from studies with the ACT of BSC for children 4 to < 6 months of age, and 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.

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 from 4 to < 6 months of age who have an R117H 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 of 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 an R117H mutation in the CFTR gene	BSC[b]	Added benefit not proven

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

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.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. Vertex Pharmaceuticals. A Phase 3, 2-Arm, Open-label Study to Evaluate the Safety and Pharmacodynamics of Long-term Ivacaftor Treatment in Subjects With Cystic Fibrosis Who Are Less Than 24 Months of Age at Treatment Initiation and Have an Approved Ivacaftor-Responsive Mutation [online]. [Accessed: 21.12.2020]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-001379-21.

4. Vertex Pharmaceuticals. A Study to Evaluate the Safety of Long-term Ivacaftor Treatment in Subjects With Cystic Fibrosis Who Are Less Than 24 Months of Age at Treatment Initiation and Have an Approved Ivacaftor-Responsive Mutation [online]. 2020 [Accessed: 21.12.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT03277196.

5. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Ivacaftor (zystische Fibrose, ab 18 Jahren mit R117H-Mutation): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2019 [Accessed: 02.12.2019]. URL: https://www.iqwig.de/download/a19-68_ivacaftor_nutzenbewertung-35a-sgb-v_v1-0.pdf.

6. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Ivacaftor (zystische Fibrose, 6 Monate bis < 18 Jahre, mit R117H-Mutation): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2020 [Accessed: 06.10.2020]. URL: https://www.iqwig.de/download/a20-52_ivacaftor_nutzenbewertung-35a-sgb-v_v1-0.pdf.

7. Vertex Pharmaceuticals (Ireland). Ivacaftor (Kalydeco): Dossier zur Nutzenbewertung gemäß § 35a SGB V; Modul 4 G [online]. 2020 [Accessed: 09.02.2021]. URL: https://www.g-ba.de/downloads/92-975-3795/2020-06-24_Modul%204G_Ivacaftor.pdf.

8. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Ivacaftor (zystische Fibrose, 12 bis < 24 Monate, mit Gating-Mutationen): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2019 [Accessed: 02.12.2019]. URL: https://www.iqwig.de/download/a19-69_ivacaftor_nutzenbewertung-35a-sgb-v_v1-0.pdf.

9. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Ivacaftor (zystische Fibrose, 6 bis < 12 Monate, mit Gating-Mutationen): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2020 [Accessed: 18.03.2020]. URL: https://www.iqwig.de/download/a19-105_ivacaftor_nutzenbewertung-35a-sgb-v_v1-0.pdf.

10. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Ivacaftor (zystische Fibrose, 4 bis < 6 Monate, mit Gating-Mutationen): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. 2020: [Soon available under: https://www.iqwig.de/projekte/a20-100.html].

11. Vertex Pharmaceuticals (Ireland). Ivacaftor (Kalydeco); Dossier zur Nutzenbewertung gemäß § 35a SGB V; Modul 4D [online]. 2019 [Accessed: 08.02.2021]. URL: https://www.g-ba.de/downloads/92-975-3211/2019-08-29_Modul4D_Ivacaftor.pdf.

The full report (German version) is published under https://www.iqwig.de/en/projects/a20-99.html.