IQWiG Reports – Commission No. A19-67

Ivacaftor (cystic fibrosis, 2 years and older, with gating mutations) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Ivacaftor (zystische Fibrose, ab 2 Jahre, mit Gating-Mutationen) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 November 2019). 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.

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

Ivacaftor (cystic fibrosis, 2 years and older, with gating mutations) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:

Federal Joint Committee

Commission awarded on:

28 August 2019

Internal Commission No.:

A19-67

Address of publisher:

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Keywords: ivacaftor, cystic fibrosis, child – preschool, benefit assessment, NCT01705145, NCT01946412, NCT02742519, NCT00909532, NCT00909727

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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 was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 28 August 2019.

Research question

The aim of the present report is the assessment of the added benefit of ivacaftor in comparison with the appropriate comparator therapy (ACT) best supportive care (BSC) in patients with cystic fibrosis (CF) aged 2 years and older and weighing between 7 kg and less than 25 kg who have one of the following gating (class III) mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R.

Table 2: Research questions of the benefit assessment of ivacaftor

Subindication	**ACT**[a]
Patients with cystic fibrosis aged 2 years and older and weighing between 7 kg and less than 25 kg who have one of the following gating (class III) mutations in the CFTR gene: G551D, G551S, G1244E, G1349D, G178R, S1251N, S1255P, S549N or S549R	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; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee	

The company named BSC as ACT and thus followed 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 the added benefit.

Results

The company did not identify any relevant RCTs for the comparison of ivacaftor versus the ACT BSC in the present therapeutic indication. For this reason, it presented results from the 2 single-arm studies VX11-770-108 und VX11-770-109 (extension study of VX11-770-108), which were to include children with CF who are 2 through 5 years of age and have one of the following CFTR gating mutations in at least one allele: G551D, G551S, G970R G1244E, G1349D, G178R, S1251N, S1255P, S549N, S549R. VX11-770-108 was a 2-part study (Part A

and B), with Part B lasting 24 weeks. This part of the study and the extension study VX11-770-109 were considered by the company for the benefit assessment. The company did not search for data on the ACT. Since the studies VX11-770-108 and VX11-770-109 were only single-arm studies, the company additionally referred to 3 RCTs in older patients (aged 6 years and older). From the company's point of view, it would be possible to transfer these data to children aged 2 years and older (7 kg to < 25 kg) and use them for the derivation of an added benefit. It justified this with a comparability of mechanism of action of the intervention, of manifestation of the disease and of efficacy and safety of ivacaftor, which it considered sufficient for children aged 2 years and older (7 kg to < 25 kg) and patients aged 6 years and older. According to the company, the evidence on patients aged 6 years and older can therefore be used for the derivation of an added benefit in children aged 2 years and older (7 kg to < 25 kg). The studies VX12-770-111, VX08-770-102 and VX08-770-103 on patients aged 6 years and older are subject of the dossier assessments on commissions A19-65 and A19-66.

Transfer of the added benefit not possible

The company's approach to transfer study results from older patients to the population relevant for the present benefit assessment is comprehensible due to the lack of directly comparative data in children aged 2 years and older (7 kg to < 25 kg). The concrete approach adopted by the company is unsuitable for this, however. An added benefit of ivacaftor versus the ACT in children aged 2 years and older (7 kg to < 25 kg) cannot be derived from the data presented by the company for the following reasons:

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

The VX12-770-111 study is a randomized crossover study with a treatment duration of 8 weeks. It included patients aged 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.

The studies VX08-770-102 and VX08-770-103 are RCTs with a treatment duration of 48 weeks. These studies included patients aged 12 years and older (VX08-770-102) and from 6 to 11 years (VX08-770-103) with the gating mutation G551D. The transferability of the data from these 2 studies to children aged 2 years and older (7 kg to < 25 kg) is inadequate for the following reasons:

- Different effects of ivacaftor versus BSC depending on disease stage
  - CF is a progressive disease. Hence, the greater the age difference between the population to be assessed and the population from which the transfer is to be made, the more questionable the transferability of results appears. The data presented on the 2 studies VX08-770-102 and VX08-770-103 show differences in demographic and clinical characteristics of the populations included. In addition, there are different effects of ivacaftor versus the ACT BSC 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 it is not meaningful to transfer results of the study population from the VX08-770-102 study to even younger children, i.e. children aged 2 years and older (7 kg to < 25 kg). This is a reason against the transferability of effects from the VX08-770-102 study (patients aged 12 years and older) to children aged 2 years and older (7 kg to < 25 kg).

- Lack of data for the assessment of the comparability of the outcomes of the studies VX11-770-108 and VX11-770-109 with study VX08-770-103

  Due to a lack of data, it was not possible to assess the comparability for the following important parameters:

  - The studies used by the company used different operationalizations for pulmonary exacerbation, a key patient-relevant outcome in the therapeutic indication of CF. For this outcome, there is no processing of the data based on comparable operationalizations for the studies VX11-770-108, VX11-770-109 and VX08-770-103. A transfer of the results from the VX08-770-103 study to children aged 2 years and older (7 kg to < 25 kg) is therefore inadequate.
  - No data for a comparison are available on lung function parameters for the different age groups. The proportion of children in the studies with children aged 2 to 5 years for whom the forced expiratory volume in 1 second (FEV1) was recorded was too small to produce interpretable results. The lung clearance index (LCI) was not recorded at all in the studies VX11-770-108 and VX11-770-109, and was only recorded in 2 of 38 children in the VX08-770-103 study.

  Regardless of whether transferability of the results from the VX08-770-103 study to children aged 2 years and older (7 kg to < 25 kg) is possible, based on the outcomes considered for the assessment on Commission A19-65, there were neither effects in favour nor effects to the disadvantage of ivacaftor + BSC versus BSC in the VX08-770-103 study.

- Missing data on the appropriate comparator therapy BSC
  - The company did not present any data from studies with the ACT BSC for children aged 2 years and older (7 kg to < 25 kg), so that the treatment effects of ivacaftor versus BSC cannot be estimated.

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

Based on the results presented, probability and extent of the added benefit of the drug ivacaftor in comparison with the ACT are assessed as follows:

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

Table 3: Ivacaftor – probability and extent of added benefit

Subindication	ACT[a]	Probability and extent of added benefit
Patients with CF aged 2 years and older and weighing between 7 kg and less than 25 kg who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R	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; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment in the framework of the market access in 2015. In this assessment, the G-BA had determined a non-quantifiable added benefit of ivacaftor. However, in this assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data because of the special situation for orphan drugs.

2.2 Research question

The aim of the present report is the assessment of the added benefit of ivacaftor in comparison with the ACT BSC in patients with CF aged 2 years and older and weighing between 7 kg and less than 25 kg who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R.

[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 questions of the benefit assessment of ivacaftor

Subindication	**ACT**[a]
Patients with cystic fibrosis aged 2 years and older and weighing between 7 kg and less than 25 kg who have one of the following gating (class III) mutations in the CFTR gene: G551D, G551S, G1244E, G1349D, G178R, S1251N, S1255P, S549N or S549R	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; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee	

The company named BSC as ACT and thus followed 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 the 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 of the company in the dossier:

- study lists on ivacaftor (status: 4 June 2019)
- bibliographical literature search on ivacaftor (status: 4 June 2019)
- search in trial registries for studies on ivacaftor (status: 4 June 2019)

To check the completeness of the study pool:

- search in trial registries for studies on ivacaftor (last search on 5 September 2019)

Concurring with the company, the check of the completeness of the study pool produced no relevant RCTs for the comparison of ivacaftor versus the ACT BSC in the present therapeutic indication. The company presented the RCT VX15-770-123 [3-6] in the dossier as supplementary information, but did not use it for its assessment as it had been discontinued prematurely and the preplanned study size had not been reached. This study is a randomized crossover study, which, with a planned treatment duration of 8 weeks, is too short to be included in the benefit assessment in the therapeutic indication of CF (see Section 2.7.3.2 and Appendix D of the full dossier assessment).

For the derivation of the added benefit, the company presented results from the 2 single-arm studies VX11-770-108 [7-11] and VX11-770-109 (extension study of VX11-770-108) [12-16] in children between 2 and 5 years of age. The company did not search for data on the ACT.

Since the studies VX11-770-108 and VX11-770-109 were only single-arm studies, the company additionally referred to 3 RCTs in older patients (aged 6 years and older). From the company's point of view, it would be possible to transfer these data to children aged 2 years and older (7 kg to < 25 kg) and use them for the derivation of an added benefit. It justified this with a comparability of mechanism of action of the intervention, of manifestation of the disease and of efficacy and safety of ivacaftor, which it considered sufficient for children aged 2 years and older (7 kg to < 25 kg) and patients aged 6 years and older. The company did not provide any processing of the data it considered relevant for the transfer of the results.

The company's approach to transfer study results from older patients to the population relevant for the present benefit assessment is comprehensible due to the lack of directly comparative data in children aged 2 years and older (7 kg to < 25 kg). The concrete approach adopted by the company is unsuitable for this, however. An added benefit of ivacaftor versus the ACT in children aged 2 years and older (7 kg to < 25 kg) cannot be derived from the data presented by the company. This is justified below.

Single-arm studies with ivacaftor (VX11-770-108 and VX11-770-109)

The VX11-770-108 study is a single-arm, open-label study with ivacaftor, which was to include children with CF who are 2 through 5 years of age and have one of the following CFTR gating mutations in at least one allele: G551D, G551S, G970R, G1244E, G1349D, G178R, S1251N, S1255P, S549N, S549R. The study was conducted in 2 parts (Part A and Part B). Ivacaftor granules were administered with a weight-adjusted dosage both in Part A and in Part B of the study. Both parts of the study differed in the outcomes investigated and in treatment duration. Whereas treatment in Part A was 4 days, treatment in Part B was 24 weeks. Due to the treatment duration, the company did not consider the Part A study phase for the benefit assessment, but only Part B. Treatment with ivacaftor in the study was in addition to concomitant treatment for the therapy of CF. Following the VX11-770-108 study, the children could be switched to the VX11-770-109 extension study and receive ivacaftor for an additional 84 weeks or participate in the study without ivacaftor treatment. Of the 34 children enrolled in the VX11-770-108 study, 33 switched to the ivacaftor arm of the VX11-770-109 extension study. With respect to the gating mutations, children included in the VX11-770-108 study only had the mutations G551D and S549R (G551D: 32 children, S549R: 2 children). Further information on the characteristics of the studies, the interventions, the included patients and the concomitant treatment can be found in Table 9 to Table 13 in Appendix A of the full dossier assessment.

Transfer of the added benefit not possible

In its argumentation on an added benefit of ivacaftor in the present therapeutic indication, the company referred to results from the studies VX12-770-111, VX08-770-102 and VX08-770-103 with patients aged 6 years and older. The company considered it possible to transfer the results from these 3 studies to the target population of children aged 2 years and older (7 kg to < 25 kg). The company aimed to transfer the added benefit from older patients with the same mutations to children aged 2 years and older (7 kg to < 25 kg).

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

The company presented the studies, the results of which it transferred to the present therapeutic indication for the derivation of the added benefit, in the dossier also in Module 4 B (VX12-770-111) and in Module 4 A (VX08-770-102 and VX08-770-103).

The VX12770-111 study is a randomized crossover study with a treatment duration of 8 weeks. The study included patients aged 6 years and older with the following gating mutations: G551S, G1244E, G1349D, G178R, S1251N, S1255P, S549N, S549R or G970R. With a treatment duration of 8 weeks, however, it is too short to be included in the benefit assessment in the therapeutic indication of CF. Detailed information on this study can be found in dossier assessment on Commission A19-66 [17].

The studies VX08-770-102 and VX08-770-103 are RCTs with a treatment duration of 48 weeks. These studies included patients aged 12 years and older (VX08-770-102) and from 6 to 11 years (VX08-770-103) with the gating mutation G551D. Both of these studies are subject of the dossier assessment on Commission A19-65 [18]. Information on the characteristics of the studies, the interventions and the included patients regarding these studies can be found in Table 14 to Table 16 in Appendix B of the full dossier assessment.

The company justified the transferability of the results of older patients to the target population with a comparability of mechanism of action of the intervention, of manifestation of the disease and of efficacy and safety, which it considered sufficient. The company's approach for a transfer is inadequate. The following aspects in particular are decisive for this:

- Different effects of ivacaftor versus BSC depending on disease stage
  - CF is a progressive disease. Hence, the greater the age difference between the population to be assessed and the population from which the transfer is to be made, the more questionable the transferability of results appears. The consideration of the results of the VX08-770-102 study (patients aged 12 years and older) and of the VX08-770-103 study (children aged 6 to 11 years) show differences in the demographic and clinical characteristics of the included populations, which resulted mainly from the different inclusion and exclusion criteria of the studies. Due to the different populations and following the company, no meta-analytic summary of the results from the 2 studies mentioned above was conducted in the benefit assessment on Commission A19-65. In addition, there are different effects of ivacaftor versus the ACT BSC in patient-relevant outcomes (see dossier assessment on Commission A19-65 [18]). Overall, 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 it is not meaningful to transfer results of the study population from the VX08-770-102 study to even younger children, i.e. children aged 2 years and older (7 kg to < 25 kg). This is a reason against

the transferability of the effects from the VX08-770-102 study (patients aged 12 years and older) to children aged 2 years and older (7 kg to < 25 kg).

- Lack of data for the assessment of the comparability of the outcomes of the studies VX11-770-108 and VX11-770-109 with study VX08-770-103.

  The results from the studies VX11-770-108 and VX11-770-109 in children aged 2 to 5 years and of the VX08-770-103 study in children aged 6 to 11 years are presented in Table 18 to Table 20 in Appendix C of the full dossier assessment.

  Due to a lack of data, it was not possible to assess the comparability for the following important parameters:

  - Compared with the VX11-770-103 study in children between 6 and 11 years of age, the studies VX11-770-108 and VX11-770-109 in children from 2 to 5 years of age used different operationalizations for pulmonary exacerbation, a key patient-relevant outcome in the therapeutic indication of CF. These differ both regarding the symptoms included in the operationalizations and regarding the persistence of the symptoms. An overview of the operationalizations used in the studies can be found in Table 17 in Appendix C of the full dossier assessment. The company did not provide any processing of the data according to comparable operationalizations for all 3 studies for this outcome. Each of the studies VX11-770-108 and VX11-770-109 used 2 different operationalizations, each of which resulted in notable differences in results already within one study. The cause of the differences in the results between all 3 studies regarding this outcome can therefore not be assessed. A transfer of the results from the VX08-770-103 study to children aged 2 years and older (7 kg to < 25 kg) is therefore inadequate.
  - No data for a comparison are available on lung function parameters for the different age groups. The proportion of children in the studies with children aged 2 to 5 years for whom the FEV1 was recorded was too small to produce interpretable results (20 of 34 children [about 59%] at the start of the VX11-770-108 study). The LCI was not recorded at all in the studies VX11-770-108 and VX11-770-109, and was only recorded in 2 of 38 children of the relevant subpopulation in the VX08-770-103 study.

- Missing data on the appropriate comparator therapy BSC
  - The company did not present any data from studies with the ACT BSC for children from 2 to 5 years of age, so that the treatment effects of ivacaftor versus BSC cannot be estimated. It did not address the question in the dossier why it had not conducted a literature search on the ACT.

In summary, the company's implementation of the transfer of the presented study results on patients aged 6 years and older to the target population for the derivation of the added benefit is unsuitable as the transferability of the evidence from children from 6 to 11 years of age cannot be adequately assessed due to insufficient data availability. Different effects are already shown for patients aged 12 years and older in comparison with children from 6 to 11 years of age, so

that a transfer of the results to even younger children is considered unsuitable. Regardless of whether transferability of the results is possible, based on the outcomes considered for the benefit assessment, the VX08-770-103 study provided neither effects in favour nor effects to the disadvantage of ivacaftor + BSC versus BSC (see dossier assessment on Commission A19-65).

2.4 Results on added benefit

The company did not present any suitable data for the assessment of the added benefit of ivacaftor versus the ACT BSC. This resulted in 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

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

Table 5: Ivacaftor – probability and extent of added benefit

Subindication	**ACT[a]**	**Probability and extent of added benefit**
Patients with CF aged 2 years and older and weighing between 7 kg and less than 25 kg who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R	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; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which derived a non-quantifiable added benefit without addressing its probability.

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment in the framework of the market access in 2015. In this assessment, the G-BA had determined a non-quantifiable added benefit of ivacaftor. However, in this assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data because of the special situation for orphan drugs.

2.6 List of included studies

Not applicable as the company did not present any relevant data for the benefit assessment.

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-results/projects/drug-assessment/a19-67-ivacaftor-cystic-fibrosis-2-years-and-older-with-gating-mutations-benefit-assessment-according-to-35a-social-code-book-v.12570.html.