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Ivacaftor (cystic fibrosis, 6 years and older, with G551D mutation) –

Addendum to Commission A19-65[1]

Addendum

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[1] Translation of addendum A20-04 *Ivacaftor (zystische Fibrose, ab 6 Jahre, mit G551D-Mutation) – Addendum zum Auftrag A19-65* (Version 1.0; Status: 30 January 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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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CFTR	cystic fibrosis transmembrane conductance regulator
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial

1 Background

On 7 January 2020, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A19-65 (Ivacaftor – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") presented results of the randomized controlled trials (RCTs) VX08-770-102 and VX08-770-103 for the assessment of the added benefit of ivacaftor in the treatment of cystic fibrosis in patients aged 6 years and older and weighing 25 kg or more who have the G551D gating mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. These studies were included in the benefit assessment. In the dossier assessment, the concomitant treatment used in the studies was not assessed to be a comprehensive implementation of the appropriate comparator therapy (ACT). This assessment was based in particular on the exclusion of treatment with inhaled hypertonic saline solution, a standard therapy for cystic fibrosis, mandated by the study design. In addition, there was no information on treatment adjustments in the sense of an increase in dose or frequency of the symptomatic therapy during both studies, and no information at all on prior and concomitant medication for the relevant subpopulation of the VX08-770-103 study. Hence, the certainty of conclusions of the study results was reduced both for conclusions on patients aged 12 years and older based on the VX08-770-102 study and for children between 6 and 11 years of age based on the VX08-770-103 study.

In its comments, the company presented supplementary information on concomitant antibiotic treatment in the studies VX08-770-102 and VX08-770-103, which went beyond the information provided in the dossier [3,4].

The G-BA commissioned IQWiG to present the analyses on antibiosis in the studies VX08-770-102 and VX08-770-103 at baseline and in the course of the studies, as presented in the commenting procedure.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

2.1 Antibiotic treatment in the studies VX08-770-102 and VX08-770-103

Table 1 presents the information additionally submitted by the company in its comments regarding concomitant treatment with antibiotics before the first administration of the study medication (baseline) and in the course of the studies VX08-770-102 and VX08-770-103.

Table 1: Additional information subsequently submitted by the company on the switch in antibiotic treatment in the framework of the basic therapy before the first administration of the study medication (baseline) and in the course of the study – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC

Study	**VX08-770-102 (≥ 12 years)**		**VX08-770-103 (6–11 years)**	
Treatment[a] Category	**Ivacaftor + BSC n (%)**	**Placebo + BSC n (%)**	**Ivacaftor + BSC n (%)**	**Placebo + BSC n (%)**
All patients (with or without antibiotic treatment at baseline)	**N[b] = 83**	**N[b] = 78**	**N[c] = 26**	**N[c] = 26**
No antibiotic treatment at baseline	21 (25.3)	15 (19.2)	12 (46.2)	8 (30.8)
Antibiotic treatment at baseline				
1 continued antibiotic	41 (49.4)	35 (44.9)	9 (34.6)	13 (50.0)
≥ 2 continued antibiotics	21 (25.3)	28 (35.9)	5 (19.2)	5 (19.2)
Initiation of antibiotic treatment between baseline and week 48				
Not initiated	5 (6.0)	1 (1.3)	0 (0)	1 (3.8)
Initiation of 1–3 antibiotics	45 (54.2)	20 (25.6)	15 (57.7)	14 (53.8)
Initiation of ≥ 4 antibiotics	33 (39.8)	57 (73.1)	11 (42.3)	11 (42.3)
Treatment with IV antibiotics at baseline	0 (0)	0 (0)	1 (3.8)	0 (0)
Treatment with IV antibiotics between baseline and week 48				
No treatment	60 (72.3)	41 (52.6)	21 (80.8)	18 (69.2)
1 IV antibiotic	4 (4.8)	6 (7.7)	0 (0)	0 (0)
≥ 2 IV antibiotics	19 (22.9)	31 (39.7)	5 (19.2)	8 (30.8)
Patients without antibiotic treatment at baseline	**N = 21**	**N = 15**	**N = 12**	**N = 8**
Initiation of antibiotic treatment between baseline and week 48				
Not initiated	5 (23.8)	1 (6.7)	0 (0)	1 (12.5)
Initiation of 1–3 antibiotics	11 (52.4)	6 (40.0)	8 (66.7)	4 (50.0)
Initiation of ≥ 4 antibiotics	5 (23.8)	8 (53.3)	4 (33.3)	3 (37.5)
Treatment with IV antibiotics between baseline and week 48				
No treatment	17 (81.0)	11 (73.3)	10 (83.3)	6 (75.0)
1 IV antibiotic	2 (9.5)	1 (6.7)	0 (0)	0 (0)
≥ 2 IV antibiotics	2 (9.5)	3 (20.0)	2 (16.7)	2 (25.0)

a. Information on treatment with antibiotics for systemic use and agents against mycobacteria, including all agents with any of the following methods of application: intramuscular, IV, IV bolus injection, nasal, oral, or inhaled.
b. Randomized patients: 84 (ivacaftor + BSC) vs. 83 (placebo + BSC).
c. Study participants from part B of the study; no information on the relevant subpopulation of the 18 vs. 20 patients weighing ≥ 25 kg.

BSC: best supportive care; IV: intravenous; n: number of patients in the category; N: number of patients who had received at least one dose of the study medication; in the VX08-770-103 study, this number concurs with the number of randomized patients; RCT: randomized controlled trial; vs.: versus

The information on concomitant antibiotic treatment subsequently submitted by the company confirms that adjustments to the antibiotic therapy were made in the course of the study. In the course of both studies (VX08-770-102 and VX08-770-103), for more than 95% of the patients of the total study population at least one antibiotic was added to therapy. In addition, the majority of patients who had not been treated with antibiotics before the first administration of the study medication also started antibiotic treatment during the course of both studies. For the VX08-770-103 study, however, the company only submitted data on the concomitant treatment of the total population of the study with its comments, and not on the concomitant treatment of the subpopulation relevant for the benefit assessment (patients weighing 25 kg or more).

Overall, the assessment regarding the incomplete implementation of the ACT for the present research question has not changed, however, which is mainly due to the exclusion of inhaled hypertonic saline solution, a standard therapy for cystic fibrosis, mandated by the study design (see dossier assessment A19-65 [1]).

2.2 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of ivacaftor from dossier assessment A19-65.

The following Table 2 shows the result of the benefit assessment of ivacaftor under consideration of dossier assessment A19-65 and the present addendum.

Table 2: Ivacaftor – probability and extent of added benefit

Subindication	**ACT[a]**	**Probability and extent of added benefit**
Children with cystic fibrosis between 6 and 11 years of age and weighing 25 kg or more who have the G551D gating mutation in the CFTR gene	BSC[b]	Added benefit not proven
Patients with cystic fibrosis aged 12 years and older and weighing 25 kg or more who have the G551D gating mutation in the CFTR gene	BSC[b]	Hint of minor added benefit
a. Presentation of the respective 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.

3 References

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2. Vertex Pharmaceuticals (Ireland). Ivacaftor (Kalydeco): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 29.08.2019 [Accessed: 09.01.2020]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/431/#dossier.

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4. Vertex Pharmaceuticals. Ivacaftor (Kalydeco): zusätzliche Analysen im Rahmen der Stellungnahme [unpublished]. 2019.