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Ivacaftor (combination with ivacaftor/ tezacaftor/elexacaftor; cystic fibrosis, 12 years and older, F508del mutation, MF mutation, heterozygous) –

Addendum to Commission A20-83[1]

Addendum

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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
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MF	minimal function
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 12 January 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A20-83 (Ivacaftor – Benefit assessment according to §35a Social Code Book V) [1].

Dossier assessment A20-83 on the added benefit of ivacaftor in combination with ivacaftor/tezacaftor/elexacaftor (hereinafter referred to as "ivacaftor + ivacaftor/tezacaftor/elexacaftor") in comparison with best supportive care (BSC) as the appropriate comparator therapy (ACT) in patients with cystic fibrosis (CF) aged 12 years and older who are heterozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene and have a minimal function (MF) mutation on the 2nd allele included the randomized controlled trial (RCT) VX17-445-102. For the outcomes of health-related quality of life and symptoms, as surveyed with the Cystic Fibrosis Questionnaire – Revised (CFQ-R), analyses with a mixed model for repeated measures were available to ensure consistent analysis of all CFQ-R domains and hence meaningful interpretation. In the commenting procedure [2-4], the pharmaceutical company (hereinafter "company") subsequently submitted responder analyses of the VX17-445-102 study for the outcomes of health-related quality of life and symptoms, surveyed with the CFQ-R. The G-BA therefore commissioned IQWiG with the assessment of these subsequently submitted analyses under consideration of the information provided in the dossier [5].

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 Analyses subsequently submitted for the outcomes on symptoms and health-related quality of life (each surveyed using the CFQ-R)

In accordance with the Institute's *General Methods* [6,7], the company presented post hoc analyses on 15% of the scale range conducted for the CFQ-R. For the CFQ-R with a scale range of 0 to 100 [8], 15% corresponds exactly to 15 points (responder analysis presented by the company: improvement by ≥ 15 points). According to the company [9], the response persisted throughout the 24 weeks, i.e. over the course of the study, rather than being observed only at a single time point. In this context, it is unclear whether the improvement existed at 1 documentation time point within the course of the study or at several time points.

2.2 Risk of bias

As discussed in dossier assessment A20-83, the risk of bias on the study level was rated as low for the VX17-445-102 study. The risk of bias for the subsequently submitted results using the responder analyses of the outcomes of symptoms and health-related quality of life (each surveyed using CFQ-R) is rated as low as well.

The certainty of study results is reduced for the present research question due to the ambiguities concerning the implementation of the ACT, as described in dossier assessment A20-83. For the above outcomes, at most hints, e.g. of an added benefit, can therefore be derived.

2.3 Results

Table 1 summarizes the CFQ-R results for the comparison of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC versus placebo + BSC in CF patients 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and exhibit an MF mutation.

Table 1: Results (morbidity, health-related quality of life) – RCT, direct comparison: ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC vs. placebo + BSC

Study Outcome category Outcome	IVA + IVA/TEZA/ELEXA + BSC		Placebo + BSC		Group difference
	N	Patients with event n (%)	N	Patients with event n (%)	RR[a] [95% CI]; p-value
VX17-445-102					
Morbidity					
Symptoms (CFQ-R, symptom domains, children [12 to 13 years] and adolescents or adults – pooled); improvement by ≥ 15 points[b]					
Respiratory symptoms	200	103 (51.5)	203	14 (6.9)	7.55 [4.48; 12.72]; < 0.001
Digestive symptoms	200	29 (14.5)	203	25 (12.3)	1.17 [0.71; 1.92]; 0.535
Weight[c]	185	62 (33.5)	179	32 (17.9)	1.91 [1.31; 2.77]; < 0.001
Health-related quality of life					
Health-related quality of life (CFQ-R, health-related quality of life domains, children [12 to 13 years] and adolescents or adults – pooled); improvement by ≥ 15 points[b]					
Physical functioning	200	51 (25.5)	203	12 (5.9)	4.38 [2.42; 7.94]; < 0.001
Role functioning[c]	185	30 (16.2)	179	7 (3.9)	4.17 [1.88; 9.23]; < 0.001
Vitality[c]	185	46 (24.9)	179	6 (3.4)	7.51 [3.30; 17.07]; < 0.001
Emotional functioning	200	22 (11.0)	203	8 (3.9)	2.77 [1.27; 6.07]; 0.011
Social functioning	200	34 (17.0)	203	10 (4.9)	3.48 [1.77; 6.83]; < 0.001
Body image	200	34 (17.0)	203	18 (8.9)	1.91 [1.12; 3.26]; 0.018
Eating disorders	200	22 (11.0)	203	11 (5.4)	2.06 [1.04; 4.10]; 0.040
Treatment burden	200	33 (16.5)	203	9 (4.4)	3.72 [1.83; 7.57]; < 0.001
Health perceptions[c]	185	77 (41.6)	179	10 (5.6)	7.49 [4.01; 14.00]; < 0.001

a. Generalized linear model; adjusted by age, sex, and ppFEV1 baseline value.
b. Improvement, defined as an increase in CFQ-R score by at least 15 points from baseline; it is unclear whether this improvement existed at 1 documentation time point within the 24-week course of the study or at several time points.
c. Domain for adolescents or adults; not intended for children [12 to 13 years].

BSC: best supportive care; CI: confidence interval; ELEXA: elexacaftor; IVA: ivacaftor; n: number of patients with (at least 1) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; TEZA: tezacaftor

Morbidity

Symptoms measured using the CFQ-R

Respiratory symptoms domain

In the respiratory symptoms domain, the responder analysis (improvement by at least 15 points) shows a statistically significant difference in favour of ivacaftor + ivacaftor/tezacaftor/ elexacaftor + BSC versus placebo + BSC. An effect modification by the characteristic of sex was found (see Section 2.4). However, since the results in both subgroups do not differ in extent or direction of effect from the results of the entire study population (see Section 2.5), the

characteristic of sex was disregarded in the further analysis of the respiratory symptoms domain. For the respiratory symptoms domain of the CFQ-R, this results in a hint of added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with BSC.

Digestive symptoms domain

In the digestive symptoms domain, the responder analysis (improvement by at least 15 points) shows no statistically significant difference between treatment groups. For the digestive symptoms domain of CFQ-R, this results in no hint of an added benefit of ivacaftor + ivacaftor/ tezacaftor/elexacaftor + BSC in comparison with BSC; an added benefit is therefore not proven.

Weight domain

In the weight domain, the responder analysis (improvement by at least 15 points) shows a statistically significant difference in favour of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC versus placebo + BSC. However, there is an effect modification by the characteristic of age. For the CFQ-R weight domain in patients ≥ 18 years of age, this results in a hint of added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with BSC. For patients < 18 years of age, however, no hint of added benefit was found (see Section 2.4).

Health-related quality of life surveyed using the CFQ-R

Physical functioning and social functioning domains

For each of the physical functioning and social functioning domains, the responder analysis (improvement by at least 15 points) shows a statistically significant difference in favour of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC versus placebo + BSC. However, for both domains, an effect modification by the characteristic of age was found. For each of the physical functioning and social functioning domains of the CFQ-R, this results in a hint of added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with BSC for patients aged ≥ 18 years. For patients < 18 years of age, however, no hint of added benefit was found in either case (see Section 2.4).

Role functioning, emotional functioning, body image, eating disorders, treatment burden, and health perceptions domains

For each of the domains of role functioning, emotional functioning, body image, eating disorders, treatment burden, and health perceptions, the responder analysis (improvement by at least 15 points) shows a statistically significant difference in favour of ivacaftor + ivacaftor/ tezacaftor/elexacaftor + BSC versus placebo + BSC. For each of these domains of the CFQ-R, this results in a hint of added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with BSC.

Vitality domain

For the vitality domain, the responder analysis (improvement by at least 15 points) shows a statistically significant difference in favour of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC versus placebo + BSC. An effect modification by the characteristic of sex was found (see

Section 2.4). However, since the results in both subgroups do not differ in extent or direction of effect from the results of the entire study population (see Section 2.5), the characteristic of sex was disregarded in the further analysis of the vitality domain. For the vitality domain of the CFQ-R, this results in a hint of added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with BSC.

2.4 Subgroups and other effect modifiers

According to the methods described in dossier assessment A20-83, the subsequently submitted responder analyses use the following subgroups for the outcomes of symptoms and health-related quality of life (each surveyed using CFQ-R):

- age (< 18 / ≥ 18 years)
- sex (female/male)

Table 2 presents the subgroup results for the comparison of ivacaftor + ivacaftor/tezacaftor/ elexacaftor + BSC with placebo + BSC.

Table 2: Subgroups (morbidity, health-related quality of life) – RCT, direct comparison: ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC vs. placebo + BSC (multipage table)

Study Outcome Characteristic Subgroup	IVA + IVA/TEZA/ELEXA + BSC		Placebo + BSC		Group difference	
	N	Patients with event n (%)	N	Patients with event n (%)	RR[a] [95% CI]	p-value
VX17-445-102						
Morbidity: Symptoms (CFQ-R, symptom domains)[b, c]						
Respiratory symptoms						
Sex						
Men	104	58 (55.8)	105	4 (3.8)	14.84 [5.60; 39.29]	< 0.001
Women	96	45 (46.9)	98	10 (10.2)	4.59 [2.46; 8.56]	< 0.001
Total					Interaction:	0.034
Weight[d]						
Age						
< 18 years	41	9 (22.0)	36	11 (30.6)	0.71 [0.33; 1.53]	0.388
≥ 18 years	144	53 (36.8)	143	21 (14.7)	2.54 [1.62; 3.97]	< 0.001
Total					Interaction:	0.006
Health-related quality of life (CFQ-R, domains on health-related quality of life)[b, c]						
Physical functioning						
Age						
< 18 years	56	10 (17.9)	60	7 (11.7)	1.62 [0.68; 3.83]	0.274
≥ 18 years	144	41 (28.5)	143	5 (3.5)	8.27 [3.39; 20.15]	< 0.001
Total					Interaction:	0.024
Vitality[b]						
Sex						
Men	94	40 (42.55)	96	5 (5.21)	8.10 [3.35; 19.61]	< 0.001
Women	91	37 (40.7)	83	5 (6.0)	6.79 [2.81; 16.45]	< 0.001
Total					Interaction:	0.0448
Social functioning						
Age						
< 18 years	56	5 (8.9)	60	6 (10.0)	0.93 [0.30; 2.83]	0.895
≥ 18 years	144	29 (20.1)	143	4 (2.8)	7.21 [2.61; 19.95]	< 0.001
Total					Interaction:	0.006

a. Generalized linear model; adjusted by age, sex, and ppFEV1 baseline value.
b. Improvement, defined as an increase in CFQ-R score by at least 15 points from baseline; it is unclear whether this improvement existed at 1 documentation time point within the 24-week course of the study or at several time points.
c. Symptoms and health-related quality of life domains, children [12 to 13 years] and adolescents or adults – pooled.
d. Domain for adolescents or adults; not intended for children [12 to 13 years].

Table 2: Subgroups (morbidity, health-related quality of life) – RCT, direct comparison: ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC vs. placebo + BSC (multipage table)

Study Outcome Characteristic Subgroup	IVA + IVA/TEZA/ELEXA + BSC		Placebo + BSC		Group difference	
	N	Patients with event n (%)	N	Patients with event n (%)	RR[a] [95% CI]	p-value
BSC: best supportive care; CI: confidence interval; ELEXA: elexacaftor; IVA: ivacaftor; n: number of patients with (at least 1) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; TEZA: tezacaftor						

Morbidity

Symptoms measured using the CFQ-R

Respiratory symptoms domain

For the respiratory symptoms domain, there is an effect modification by the characteristic of sex. For both subgroups, the responder analysis (improvement by at least 15 points) shows a statistically significant difference in favour of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC versus placebo + BSC. The extent for both subgroups is consistent with the result for the total study population (see Section 2.5). For the CFQ-R respiratory symptoms domain, the characteristic of age is therefore disregarded below.

Weight domain

For the weight domain, an effect modification by the characteristic of age was found. In patients ≥ 18 years of age, the responder analysis (improvement by at least 15 points) shows a statistically significant difference in favour of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC versus placebo + BSC. For the CFQ-R domain of weight in patients aged ≥ 18 years, this results in a hint of added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with BSC. In contrast, for patients aged < 18 years, no statistically significant difference was found between the treatment groups; hence, there is no proof of added benefit for ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC versus BSC for these patients.

Health-related quality of life surveyed using the CFQ-R

Physical functioning and social functioning domains

An effect modification by the characteristic of age was found for both the physical functioning and the social functioning domains. For patients ≥ 18 years of age, the responder analysis (improvement by at least 15 points) shows a statistically significant difference in favour of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC versus placebo + BSC for each of them. For each of the physical functioning and social functioning domains of the CFQ-R, this results in a hint of added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with BSC for patients aged ≥ 18 years. In contrast, for patients aged < 18 years, no statistically

significant difference was found between the treatment groups in either case; hence, there is no proof of added benefit for ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC versus BSC for these patients.

Vitality domain

There is an effect modification by the characteristic of sex for the vitality domain. For both subgroups, the responder analysis (improvement by at least 15 points) shows a statistically significant difference in favour of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC versus placebo + BSC. The extent for both subgroups is consistent with the result for the total study population (see Section 2.5). For the CFQ-R vitality domain, the characteristic of age is therefore disregarded below.

2.5 Probability and extent of added benefit

Table 3 shows the probability and extent of added benefit on the outcome level, taking into account dossier assessment A20-83. Based on the results presented in Sections 2.3. and 2.4, the extent of the respective added benefit at outcome level is estimated for the CFQ-R domains.

The company's dossier and the analyses subsequently submitted in the commenting procedure did not provide any information on the assignment of a severity grade to the CFQ-R symptom domains. Therefore, the outcomes were assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Table 3: Extent of added benefit at outcome level: ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC vs. BSC (multipage table)

Outcome category **Outcome** **Domain** **Effect modifier** **Subgroup**	**Ivacaftor + ivacaftor/tezacaftor/ elexacaftor + BSC vs. placebo + BSC** **event rate or event proportion (%)** **effect estimate [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0% RR: –	Lesser benefit/added benefit not proven
Morbidity		
Pulmonary exacerbations	Rate: 0.40 vs. 1.07 Rate ratio: 0.37 [0.25; 0.55] p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 Added benefit, extent: considerable
Hospitalization due to pulmonary exacerbations	Rate: 0.08 vs. 0.26 Rate ratio: 0.29 [0.14; 0.61] ND Probability: hint	Outcome category: serious/severe symptoms/late complications CI_u < 0.75, risk ≥ 5%[c] Added benefit, extent: major
Symptoms (CFQ-R symptom domains, improvement by ≥ 15 points)		
Respiratory symptoms	51.5% vs. 6.9% RR: 7.55 [4.48; 12.72] RR: 0.13 [0.08; 0.22][d] p < 0.001 Probability: hint	Outcome category: non-serious/ non-severe symptoms/late complications CI_u < 0.80 Added benefit, extent: considerable
Digestive symptoms	14.5% vs. 12.3% RR: 1.17 [0.71; 1.92] p = 0.535	Lesser benefit/added benefit not proven
Weight Age < 18 years	22.0% vs. 30.6% RR: 0.71 [0.33; 1.53] p = 0.388	Lesser benefit/added benefit not proven
≥ 18 years	36.8% vs. 14.7% RR: 2.54 [1.62; 3.97] RR: 0.39 [0.25; 0.62][d] p < 0.001 Probability: hint	Outcome category: non-serious/ non-severe symptoms/late complications CI_u < 0.80 Added benefit, extent: considerable

Table 3: Extent of added benefit at outcome level: ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC vs. BSC (multipage table)

Outcome category **Outcome** **Domain** **Effect modifier** **Subgroup**	**Ivacaftor + ivacaftor/tezacaftor/ elexacaftor + BSC vs. placebo + BSC event rate or event proportion (%) effect estimate [95% CI]; p-value probability**[a]	**Derivation of extent**[b]
Health-related quality of life (CFQ-R, domains on health-related quality of life, improvement by ≥ 15 points)		
Physical functioning Age < 18 years	17.9% vs. 11.7% RR: 1.62 [0.68; 3.83] p = 0.274	Lesser benefit/added benefit not proven
≥ 18 years	28.5% vs. 3.5% RR: 8.27 [3.39; 20.15] RR: 0.12 [0.05; 0.29][d] p < 0.001 Probability: hint	Outcome category: health-related quality of life $CI_u < 0.75$, risk ≥ 5% Added benefit, extent: major
Emotional functioning	11.0% vs. 3.9% RR: 2.77 [1.27; 6.07] RR: 0.36 [0.16; 0.79][d] p = 0.011 Probability: hint	Outcome category: health-related quality of life $0.75 \leq CI_u < 0$ Added benefit, extent considerable
Vitality	24.9% vs. 3.4% RR: 7.51 [3.30; 17.07] RR: 0.13 [0.06; 0.30][d] p < 0.001 Probability: hint	Outcome category: health-related quality of life $CI_u < 0.75$, risk ≥ 5% Added benefit, extent: major
Social functioning Age < 18 years	8.9% vs. 10.0% RR: 0.93 [0.30; 2.83] p = 0.895	Lesser benefit/added benefit not proven
≥ 18 years	20.1% vs. 2.8% RR: 7.21 [2.61; 19.95] RR: 0.14 [0.05; 0.38][d] p < 0.001 Probability: hint	Outcome category: health-related quality of life $CI_u < 0.75$, risk ≥ 5% Added benefit, extent: major
Role functioning	16.2% vs. 3.9% RR: 4.17 [1.88; 9.23] RR: 0.24 [0.11; 0.53][d] p < 0.001 Probability: hint	Outcome category: health-related quality of life $CI_u < 0.75$, risk ≥ 5% Added benefit, extent: major

Table 3: Extent of added benefit at outcome level: ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC vs. BSC (multipage table)

Outcome category **Outcome** **Domain** **Effect modifier** **Subgroup**	**Ivacaftor + ivacaftor/tezacaftor/ elexacaftor + BSC vs. placebo + BSC** **event rate or event proportion (%)** **effect estimate [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Body image	17.0% vs. 8.9% RR: 1.91 [1.12; 3.26] RR: 0.52 [0.31; 0.89][d] p = 0.018 Probability: hint	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ Added benefit, extent: considerable
Eating disorders	11.0% vs. 5.4% RR: 2.06 [1.04; 4.10] RR: 0.49 [0.24; 0.96][d] p = 0.040 Probability: hint	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit, extent: minor
Treatment burden	16.5% vs. 4.4% RR: 3.72 [1.83; 7.57] RR: 0.27 [0.13; 0.55][d] p < 0.001 Probability: hint	Outcome category: health-related quality of life $CI_u < 0.75$, risk ≥ 5% Added benefit, extent: major
Health perceptions	41.6% vs. 5.6% RR: 7.49 [4.01; 14.00] RR: 0.13 [0.07; 0.25][d] p < 0.001 Probability: hint	Outcome category: health-related quality of life $CI_u < 0.75$, risk ≥ 5% Added benefit, extent: major
AEs		
SAEs	9.9% vs. 8.0% RR: 1.24 [0.66; 2.33] p = 0.533	Greater/lesser harm not proven
Discontinuation due to AEs	1.0% vs. 0% RR: 4.98 [0.24; 102.99] p = 0.212	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Estimations of effect size are made depending on the outcome category, with different limits based on the upper limit of the confidence interval (CI_u).
c. Hospitalization due to pulmonary exacerbations in 7 patients in the intervention arm (3.5%) and 27 patients in the comparator arm (13.3%)
d. IQWiG calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CI: confidence interval; CI_u: upper limit of confidence interval; MD: mean difference; ND: no data; RR: relative risk; SAE: serious adverse event

2.6 Overall conclusion on added benefit

Table 4 summarizes the results which were factored into the overall conclusion on the extent of added benefit.

Table 4: Favourable and unfavourable effects from the assessment of ivacaftor + ivacaftor/tezacaftor/elexacaftor in comparison with BSC

Favourable effects	**Unfavourable effects**
Serious/severe symptoms/late complications ▪ Hospitalization due to pulmonary exacerbations: hint of added benefit – extent: major	–
Non-serious/non-severe symptoms/late complications ▪ Pulmonary exacerbations: hint of an added benefit – extent: considerable ▪ Symptoms ▫ Respiratory symptoms domain: hint of added benefit – **extent: considerable** ▫ Weight[a] - Age ≥ 18 years: hint of added benefit – **extent: considerable**	–
Health-related quality of life ▪ Domains of physical functioning, social functioning ▫ Age ≥ 18 years: hint of added benefit – **extent: major** ▪ Domains of vitality[a], role functioning[a], **treatment burden**, health perceptions[a]: hint of added benefit – **extent: major** ▪ **Domains of emotional functioning, body image: hint of added benefit – extent: considerable** ▪ Eating disorders domain: hint of added benefit – **extent minor**	–
The results presented in **bold** stem from the analyses subsequently submitted by the company in the commenting procedure. a. CFQ-R domain documented only in adolescents or adults because it is not intended for children [12 to 13 years]. BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire - Revised	

When compared to the results of dossier assessment A20-83, 2 additional favourable effects (emotional functioning and body image domains) are found for the outcome of health-related quality of life after including the data subsequently submitted in the commenting procedure. Consequently, favourable effects of ivacaftor + ivacaftor/tezacaftor/elexacaftor in comparison with BSC are now found in all health-related quality of life domains. Additionally, CFQ-R domains (symptoms and health-related quality of life) which, in dossier assessment A20-83, exhibited favourable, but non-quantifiable effects of ivacaftor + ivacaftor/tezacaftor/elexacaftor in comparison with BSC, the added benefit on the outcome level can now be quantified. In 1 domain (eating disorders), a hint of added benefit was found with an extent of minor. All of the other domains show hints of either considerable or major added benefit. In 3 domains

(physical functioning, social functioning, and weight), the added benefit is limited to the subgroup of patients ≥ 18 years.

For hospitalization due to pulmonary exacerbations, there is a hint of major added benefit (as described in dossier assessment A20-83); additionally, there is a hint of considerable added benefit for pulmonary exacerbations.

Overall, exclusively favourable effects of ivacaftor + ivacaftor/tezacaftor/elexacaftor in combination with BSC were found; consistent with the findings of dossier assessment A20-83, this results in a hint of major added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor versus the ACT of BSC for CF patients 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation.

2.7 Summary

The data subsequently submitted by the company in the commenting procedure did not change the conclusion on the added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor when compared to the conclusion drawn in dossier assessment A20-83.

Table 5 shows the result of the benefit assessment of ivacaftor + ivacaftor/tezacaftor/ elexacaftor, taking into account both dossier assessment A20-83 and the present addendum.

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

Indication	**ACT**[a]	**Probability and extent of added benefit**
CF patients 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation	BSC[b]	Hint of major added benefit

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; MF: minimal function

The G-BA decides on the added benefit.

3 References

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