Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Ivacaftor/ Tezacaftor/ Elexacaftor (new therapeutic indication: cystic fibrosis, combination regimen with ivacaftor, 6 to 11 years (heterozygous for F508del and MF mutation))

of 4 August 2022

At its session on 4 August 2022, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of Ivacaftor/ Tezacaftor/ Elexacaftor in accordance with the resolution of 19 November 2021:

Ivacaftor/ Tezacaftor/ Elexacaftor

Resolution of: 4 August 2022
Entry into force on: 4 August 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 7 January 2022):

Kaftrio is indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

Therapeutic indication of the resolution (resolution of 4 August 2022):

Kaftrio is indicated in a combination treatment with ivacaftor for the treatment of cystic fibrosis in children aged 6 to 11 years who are heterozygous for an F508del mutation in the CFTR gene and carry a minimal function mutation on the second allele.

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

Children aged 6 to 11 years with cystic fibrosis who are heterozygous for the F508del mutation in the CFTR gene and carry a minimal function mutation on the second allele

Appropriate comparator therapy for ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor:

Best supportive care

Best Supportive Care (BSC) is defined as the therapy that ensures the best possible, patient-individual optimised, supportive treatment to alleviate symptoms and improve the quality of life (in particular antibiotics for pulmonary infections, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy (as defined in the Remedies Directive), making full use of all possible dietary measures).

Extent and probability of the additional benefit of Ivacaftor/ Tezacaftor/ Elexacaftor in combination with ivacaftor compared to the appropriate comparator therapy:

Indication of a considerable additional benefit

Study results according to endpoints:[1]

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	↑↑	Advantages in the endpoints of pulmonary exacerbations, $LCI_{2,5}$, BMI and BMI z score, and the respiratory system and gastrointestinal symptoms domains of the CFQ-R
Health-related quality of life	↑↑	Advantages in the domains of social limitations of the CFQ-R
Side effects	↔	No relevant differences for the benefit assessment in the endpoints of SAEs and discontinuation due to AEs; in detail, advantage in the endpoint of abdominal pain.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

VX19-445-116 study (parallel, multicentre, double-blind, randomised, controlled over 24 weeks with 121 patients):

Ivacaftor/ tezacaftor/ elexacaftor + ivacaftor (IVA/TEZ/ELX + IVA) + best supportive care (BSC) vs placebo + best supportive care (placebo + BSC)

Mortality

Endpoint	IVA/ TEZ/ ELX + IVA + BSC		Placebo + BSC		IVA/ TEZ/ ELX + IVA vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a)]
Overall mortality	60	0 (0.0)	61	0 (0.0)	-

Morbidity

Endpoint	IVA/ TEZ/ ELX + IVA + BSC	Placebo + BSC	IVA/ TEZ/ ELX + IVA vs placebo

[1] Data from the dossier assessment of the IQWiG (A21-15 and A22-21) unless otherwise indicated.

	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a)]
Pulmonary exacerbations[b)]	60	1 (1.7)	61	16 (26.2)	0.06 [0.01; 0.46]; < 0.001
Severe pulmonary exacerbations[c)]	60	0 (0.0)	61	3 (4.9)	0.15 [0.01; 2.75]; 0.094[d)]

Endpoint	**IVA/ TEZ/ ELX + IVA + BSC**			**Placebo + BSC**			**IVA/ TEZ/ ELX + IVA vs placebo**
	N[e)]	Values at the start of the study MV (SD)	Mean change to week 24 MV (SE)[f)]	N[e)]	Values at the start of the study MV (SD)	Mean change to week 24 MV (SE)[f)]	MD [95% CI] p value[g)] Hedges' g
Domains for the symptomatology of the Cystic Fibrosis Questionnaire - Revised (CFQ-R)[h)]							
Respiratory system	60	85.69 (11.69)	5.94 (1.61)	61	82.65 (14.13)	0.47 (1.59)	5.47 [0.98; 9.96]; 0.017 0.44 [0.08; 0.80]
Gastrointestinal symptoms	60	78.33 (22.82)	6.85 (2.65)	61	74.86 (26.29)	-1.81 (2.62)	8.66 [1.24; 16.07]; 0.023 0.42 [0.06; 0.78]
Weight problems	*Domain not provided in questionnaire for children (6 to 11 years)*						
Domains for the symptomatology of CFQ-R[h)] Parent/ caregiver version *(presented additionally)*							
Respiratory system	60	85.44 (13.75)	9.87 (1.58)	61	83.61 (15.33)	1.14 (1.56)	8.73 [4.31; 13.15]; < 0.001 0.71 [0.34; 1.08]
Gastrointestinal symptoms	60	76.30 (20.91)	7.06 (1.92)	61	70.86 (20.40)	3.30 (1.91)	3.76 [-1.63; 9.15]; 0.170
Weight problems	60	63.89 (36.97)	18.02 (3.83)	61	65.03 (36.22)	1.31 (3.79)	16.71 [6.00; 27.43]; 0.003 0.56 [0.20; 0.93]
Forced expiratory one second volume (FEV_1%)							
FEV_1[h)] (absolute change)	59	91.41 (13.83)	9.48 (1.46)[i)]	59	87.20 (15.84)	-1.53 (1.46)[i)]	11.01 [6.89; 15.12]; < 0.001[j)]
Lung Clearance Index ($LCI_{2,5}$)							
$LCI_{2,5}$[k)] (absolute change)	60	10.26 (2.22)	-2.29 (0.16)[i)]	61	9.75 (1.95)	-0.02 (0.16)[i)]	-2.26 [-2.71; -1.81]; < 0.001[j)]
Body Mass Index (BMI)							

BMI ([kg/m^2], absolute change)	59	16.33 (1.84)	0.92 (0,10)[l)]	59	16.11 (2.32)	0.26 (0,10)[l)]	0.66 [0.37; 0.95]; < 0.001[m)]
BMI (age-related z-score, absolute change)	59	-0.17 (0.85)	0.31 (0,05)[l)]	59	-0.39 (0.92)	0.03 (0,05)[l)]	0.28 [0.14; 0.41]; < 0.001[m)]
Sweat chloride concentration[n)] *(presented additionally)*							
Sweat chloride concentration ([mmol/l], absolute change)	60	102.84 (9.98)	-58.91 (14.62)	61	102.57 (8.55)	-3.90 (9.98)	-51.18 [-55.31; -47.05] < 0.0001 -4.46 [-5.13; -3.79]

Health-related quality of life

Endpoint	**IVA/ TEZ/ ELX + IVA + BSC**			**Placebo + BSC**			**IVA/ TEZ/ ELX + IVA vs placebo**
	N[e)]	Values at the start of the study MV (SD)	Mean change to week 24 MV (SE)[f)]	N[e)]	Values at the start of the study MV (SD)	Mean change to week 24 MV (SE)[f)]	MD [95% CI] p value[g)] Hedges' g
Domains for the health-related quality of life of the CFQ-R[h)]							
Physical well-being	60	86.17 (13.58)	4.33 (1.57)	61	80.51 (22.69)	0.44 (1.55)	3.89 [-0.50; 8.28]; 0.082
Emotional state	60	78.06 (11.43)	4.36 (1.50)	61	76.74 (13.94)	1.83 (1.49)	2.53 [-1.68; 6.73]; 0.236
Social limitations	60	65.74 (15.60)	3.23 (1.68)	61	67.62 (17.57)	-1.88 (1.66)	5.12 [0.43; 9.81]; 0.033 0.39 [0.03; 0.75]
Vitality	*Domain not provided in questionnaire for children (6 to 11 years)*						
School problems	*Domain not provided in questionnaire for children (6 to 11 years)*						
Body image	60	84.63 (20.87)	8.39 (2.19)	61	84.34 (20.32)	4.45 (2.16)	3.94 [-2.18; 10.06]; 0.205
Eating disorders	60	81.67 (23.13)	7.76 (2.16)	61	79.60 (23.15)	2.70 (2.14)	5.06 [-0.97; 11.10]; 0.099
Burden of therapy	60	72.22 (18.69)	3.11 (2.03)	61	74.13 (20.26)	3.21 (2.01)	-0.09 [-5.77; 5.58]; 0.974
Subjective health assessment	*Domain not provided in questionnaire for children (6 to 11 years)*						
Domains for the health-related quality of life of the CFQ-R[h)] Parent/ caregiver version *(presented additionally)*							
Physical well-being	60	90.49 (10.88)	2.06 (1.30)	61	85.31 (16.45)	-1.14 (1.28)	3.21 [-0.42; 6.83]; 0.083

Emotional state	60	85.22 (10.57)	1.53 (1.33)	61	82.84 (16.12)	-0.23 (1.31)	1.76 [-1.94; 5.47]; 0.348
Social limitations	*Domain not provided in the questionnaire for parents/ caregivers*						
Vitality	60	74.11 (13.05)	3.56 (1.51)	61	70.82 (16.29)	0.43 (1.50)	3.13 [-1.10; 7.36]; 0.146
School problems[o)]	60	80.83 (17.58)	2.09 (1.83)	61	78.96 (18.42)	0.78 (1.81)	1.31 [-3.80; 6.43]; 0.612
Body image	60	78.70 (19.55)	7.77 (1.92)	61	81.24 (22.18)	2.15 (1.90)	5.62 [0.27; 10.98]; 0.040 0.38 [0.02; 0.74]
Eating disorders	60	79.31 (23.63)	5.81 (2.53)	61	76.23 (27.63)	1.89 (2.46)	3.92 [-3.11; 10.94]; 0.272
Burden of therapy	60	59.26 (20.93)	6.61 (2.19)	61	60.11 (20.12)	2.41 (2.16)	4.20 [-1.92; 10.31]; 0.177
Subjective health assessment	60	77.96 (15.65)	5.28 (1.96)	61	70.31 (19.32)	3.05 (1.94)	2.23 [-3.25; 7.71]; 0.421

Side effects

Endpoint	**IVA/ TEZ/ ELX + IVA + BSC**		**Placebo + BSC**		**IVA/ TEZ/ ELX + IVA vs placebo**
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a)]
AEs (presented additionally)[p)]	60	48 (80.0)	61	54 (88.5)	-
SAEs[p)]	60	4 (6.7)	61	6 (9.8)	0.68 [0.20; 2.28]; 0.569
Discontinuation due to AEs[p)]	60	1 (1.7)	61	0 (0.0)	-[q)]; 0.367
Abdominal pain (PT, AEs)	60	5 (8.3)	61	17 (27.9)	0.30 [0.12; 0.76]; 0.006

a. RR, CI (asymptotic) and p value (own calculation, unconditional exact test, CSZ method).
b. Assessed via the AEs as "Infectious pulmonary exacerbation of cystic fibrosis" (PT)
c. Assessed via the SAEs as "Infectious pulmonary exacerbation of cystic fibrosis" (PT)
d. Own calculation: The correction factor 0.5 was used in both study arms when calculating effect and CI.
e. Number of patients who were taken into account in the evaluation for calculating the effect estimate; the values at start of study can be based on other patient numbers.
f. Mean change up to week 24 from MMRM
g. MMRM; adjusted for $LCI_{.5}$ and body weight at the start of the study; additionally study time point, treatment×study time point as fixed effects in the model. The effect represents the difference between the treatment groups of the changes averaged over the course of the study (up to week 24) between the respective time of measurement and the start of the study.
h. Higher (increasing) values mean better symptomatology/ health-related quality of life; positive effects (intervention minus control) mean an advantage for the intervention (scale range 0 to 100).
i. Mean change up to week 24: MV (SE) from MMRM.
j. The effect represents the difference between the treatment groups of the changes averaged over the course of the study (up to week 24) between the respective time of measurement and the start of the study.
k. Lower (decreasing) values mean better symptomatology; negative effects (intervention minus control) mean an advantage for the intervention.
l. Change at week 24: MV (SE) from MMRM.

m. Effect represents the difference in changes between the treatment groups from the start of the study up to week 24.
n. Data from the module 4 of the pharmaceutical company's dossier
o. Designated as a role functioning by the pharmaceutical company in module 4 A
p. Without PT "Infectious pulmonary exacerbation of cystic fibrosis"
q. Effect estimate and 95% CI cannot be interpreted meaningfully

Abbreviations used:
BSC: Best supportive care; CFQ-R: Cystic fibrosis questionnaire – revised; ELX: elexacaftor; IVA: ivacaftor; CI: confidence interval; LCI: Lung Clearance Index; MD: mean difference; MMRM: mixed model for repeated measures; MV: mean value; n: number of patients with (at least 1) event; N: number of patients evaluated; PT: preferred term; RCT: randomised controlled trial; RR: relative risk; SD: standard deviation; SE: standard error; SAE: serious adverse event; TEZ: tezacaftor; AE: adverse event; vs = versus

2. Number of patients or demarcation of patient groups eligible for treatment

Children aged 6 to 11 years with cystic fibrosis who are heterozygous for the F508del mutation in the CFTR gene and carry a minimal function mutation on the second allele

approx. 230 patients

3. Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Kaftrio (active ingredient: ivacaftor/ tezacaftor/ elexacaftor) at the following publicly accessible link (last access: 15 June 2022):

https://www.ema.europa.eu/en/documents/product-information/kaftrio-epar-product-information_en.pdf

Treatment with ivacaftor should only be initiated and monitored by doctors experienced in the therapy of children with cystic fibrosis.

4. Treatment costs

Annual treatment costs:

Children aged 6 to 11 years with cystic fibrosis who are heterozygous for the F508del mutation in the CFTR gene and carry a minimal function mutation on the second allele

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Ivacaftor/ tezacaftor/ elexacaftor	€ 156,562.19
+ ivacaftor	€ 82,914.18 - € 82,970.63
Total:	€ 239,476.37 - € 239,532.81
+ best supportive care	Different from patient to patient
Appropriate comparator therapy:	
Best supportive care	Different from patient to patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 July 2022)

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 4 August 2022.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 4 August 2022

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken