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 in subjects aged 12 years and older (heterozygous for F508del and gating mutation (including R117H))

of 19 November 2021

At its session on 19 November 2021, 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 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 18 February 2021:

Ivacaftor/ tezacaftor/ elexacaftor

Resolution of: 19 November 2021
Entry into force on: 19 November 2021
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 26 April 2021):

Kaftrio is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of cystic fibrosis (CF) in patients aged 12 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 19 November 2021):

Kaftrio is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of cystic fibrosis (CF) in subjects aged 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and carry a gating mutation (including R117H) on the second allele.

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

Subjects aged 12 years and older with cystic fibrosis who are heterozygous for the F508del mutation in the CFTR gene and carry a gating mutation (including R117H) on the second allele

Appropriate comparator therapy:

Ivacaftor

Extent and probability of the additional benefit of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor compared to the appropriate comparator therapy:

An additional benefit is not proven.

Study results according to endpoints:[1]

Subjects aged 12 years and older with cystic fibrosis who are heterozygous for the F508del mutation in the CFTR gene and carry a gating mutation (including R117H) on the second allele

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	There are no assessable data.
Morbidity	n.a.	There are no assessable data.
Health-related quality of life	n.a.	There are no assessable data.
Side effects	n.a.	There are no assessable data.

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

VX18-445-104 study: Ivacaftor/ tezacaftor/ elexacaftor + ivacaftor versus ivacaftor (RCT, 8 weeks) – *presented additionally*

Endpoint category **Endpoint**	**Intervention** **Ivacaftor/ tezacaftor/ elexacaftor + ivacaftor[a]**		**Control** **Ivacaftor[a]**		**Intervention versus control**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95%-CI]; p-value**
Mortality					
There were no deaths					
Morbidity					
Pulmonary exacerbations	No usable data available[b]				
Severe pulmonary exacerbations[c]	50	2 (4.0)	45	4 (8.9)	0.45 [0.09; 2.34]; 0.343[d]
Symptomatology - Cystic Fibrosis Questionnaire-Revised (CFQ-R)[e, f]					
Respiratory system	50	14 (28.0)	45	6 (13.3)	2.10 [0.88; 5.00]; 0.094[g]

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A21-71) unless otherwise indicated.

Gastrointestinal symptoms	50	6 (12.0)		45	1 (2.2)		5.40 [0.68; 43.15]; 0.112[g]
Weight problems[h]	46	2 (4.3)		42	7 (16.7)		0.26 [0.06; 1.19]; 0.082[g]
Endpoint category Endpoint	**Intervention Ivacaftor/ tezacaftor/ elexacaftor + ivacaftor[a]**			**Control Ivacaftor[a]**			**Intervention versus control**
	N[h]	**Values at start of study MV (SD)**	**Change at end of study MV (SE)[i]**	**N[h]**	**Values at start of study MV (SD)**	**Change at end of study MV (SE)[i]**	**MD [95% CI]; p-value[i]**
Morbidity							
FEV_1 %							
FEV_1[j] (absolute change)	42	66.02 (14.77)	5.57 (0.80)	42	68.11 (16.64)	−0.18 (0.81)	5.75 [3.48; 8.02]; < 0.001
Body Mass Index (BMI)							
BMI ([kg/m²] absolute change)	40	23.71 (3.76)	0.38 (0.09)	39	22.91 (3.39)	0.21 (0.09)	0.16 [-0.10; 0.42]; 0.214
BMI (z-score, absolute change[k])	6	-0.08 (1.01)	0.13 (0.10)	9	-0.13 (0.81)	0.08 (0.08)	0.05 [-0.24; 0.33]; 0.730
Sweat chloride concentration (presented additionally)[2]							
Absolute change [mmol/l]	50	59.85 (23.26)	-21.39 (22.46)	45	47.58 (19.07)	3.43 (13.24)	-19.99 [-25.41; -14.57]; < 0.001

[2] Data from the dossier

Endpoint category Endpoint	Intervention Ivacaftor/ tezacaftor/ elexacaftor + ivacaftor[a]		Control Ivacaftor[a]		Intervention versus control
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95%-CI]; p-value
Health-related quality of life					
Cystic Fibrosis Questionnaire-Revised (CFQ-R)[e,f]					
Physical functioning	50	8 (16.0)	45	3 (6.7)	2.40 [0.68; 8.50]; 0.175[g]
Emotional functioning	50	5 (10.0)	45	1 (2.2)	4.50 [0.55; 37.08]; 0.162[g]
Vitality[l]	46	5 (10.9)	42	6 (14.3)	0.76 [0.25; 2.31]; 0.630[g]
Social functioning	50	4 (8.0)	45	3 (6.7)	1.20 [0.28; 5.07]; 0.804[g]
Role functioning[g]	46	3 (6.5)	42	5 (11.9)	0.55 [0.14; 2.15]; 0.389[g]
Body image	50	3 (6.0)	45	10 (22.2)	0.27 [0.08; 0.92]; 0.036[g]
Eating disturbances	50	1 (2.0)	45	5 (11.1)	0.18 [0.02; 1.48]; 0.111[g]
Treatment Burden	50	9 (18.0)	45	1 (2.2)	8.10 [1.07; 61.45]; 0.043[g]
Overall health perception	46	11 (23.9)	42	5 (11.9)	2.01 [0.76; 5.30]; 0.159[g]
Side effects[m]					
AE (presented additionally)	50	35 (70.0)	45	26 (57.8)	-
SAE	50	3 (6.0)	45	1 (2.2)	2.70 [0.29; 25.04]; 0.382[d]
Discontinuation due to AE	50	0 (0)	45	1 (2.2)	0.30 [0.01; 7.20]; 0.358[n]

a. Treatment was carried out in view of basic medication.
b. No eligible operationalisation available
c. Collected as "infectious pulmonary exacerbation of cystic fibrosis" (PT, SAE); the operationalisation of PT as a serious event is comparable to the operationalisation "hospitalisation due to pulmonary exacerbations", used in previous benefit assessments, which is why this is presented here as an alternative morbidity endpoint
d. From four field table
e. For the CFQ-R, the pharmaceutical company presents post hoc analyses carried out at 15% of the scale range. For the CFQ-R with a scale range from 0 to 100, the 15% corresponds to exactly 15 points;

improvement is defined as an increase in the CFQ-R score by at least 15 points in week 8 compared to baseline

f. Children (12 to 13 years) and adolescents or adult patients pooled

g. Log-binomial model with treatment group as variable

h. 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.

i. MMRM adjusted for baseline FEV_1%, baseline sweat chloride, treatment, time of study, treatment×time of study as fixed effects; effect represents the difference between treatment groups of changes, averaged over the course of the study between the respective time of measurement and start of study

j. Positive effects (intervention minus control) mean an advantage for the intervention.

k. Only for patients ≤ 20 years.

m. Without PT "Infectious pulmonary exacerbation of cystic fibrosis"

n. IQWiG calculation

Abbreviations used:

BMI: Body Mass Index; CFQ-R: cystic fibrosis questionnaire – revised; CI: confidence interval; MD: mean difference; MMRM: mixed model with repeated measures; MV: mean value; n: number of patients with (at least 1) event; N: number of patients evaluated; n. c.: not calculable; PT: preferred term; RCT: randomised controlled trial; RR: relative risk; SD: standard deviation; SE: standard error; SAE: serious adverse event; AE: adverse event

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

Subjects aged 12 years and older with cystic fibrosis who are heterozygous for the F508del mutation in the CFTR gene and carry a gating mutation (including R117H) on the second allele

approx. 133 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 (combination of active ingredients: ivacaftor/ tezacaftor/ elexacaftor) at the following publicly accessible link (last access: 11 October 2021): https://www.ema.europa.eu/en/documents/product-information/kaftrio-epar-product-information_en.pdf

Treatment with ivacaftor/ tezacaftor/ elexacaftor should only be initiated and monitored by doctors experienced in treating adolescents and adult patients with cystic fibrosis.

4. Treatment costs

Annual treatment costs:

Subjects aged 12 years and older with cystic fibrosis who are heterozygous for the F508del mutation in the CFTR gene and carry a gating mutation (including R117H) on the second allele

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Elexacaftor/ tezacaftor/ ivacaftor	€ 158,139.51
+ ivacaftor	€ 82,912.62
Total:	€ 241,052.13
Appropriate comparator therapy:	
Ivacaftor	€ 165,825.24

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 1 November 2021)

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 19 November 2021.

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

Berlin, 19 November 2021

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

Prof. Hecken