Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Ivacaftor/Tezacaftor/Elexacaftor (Exceeding the € 50 Million Limit, Cystic Fibrosis, Combination Treatment with Ivacaftor in Patients 12 Years and Older (Heterozygous for F508del and MF Mutation))

of 18 February 2021

At its session on 18 February 2021, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (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 on DD Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient ivacaftor/tezacaftor/elexacaftor as follows:

Ivacaftor/tezacaftor/elexacaftor

Resolution of: 18 February 2021
Entry into force on: 18 February 2021
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 21 August 2020):

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 are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene or heterozygous for F508del in the CFTR gene with a minimal function (MF) mutation.

Therapeutic indication of the resolution (resolution of 18 February 2021):

Kaftrio is used as a combination regimen with ivacaftor 150 mg tablets for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are heterozygous for F508del in the CFTR gene with a minimal function (MF) mutation.

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

Patients aged 12 years and older with cystic fibrosis who are heterozygous for a F508del mutation in the CFTR gene as well as a mutation with minimal function (MF) on the second allele

Appropriate comparator therapy:

Best supportive care

Extent and probability of the additional benefit of ivacaftor in combination with ivacaftor/tezacaftor/elexacaftor compared with best supportive care:

Hint for a major additional benefit

Study results according to endpoints:[1]

Study VX17-445-102 (parallel, multi-centre, double-blind, randomised controlled over 24 weeks): Ivacaftor/tezacaftor/elexacaftor + ivacaftor (IVA/TEZ/ELX + IVA) + best supportive care (BSC) vs placebo + best supportive care (placebo + BSC)

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No differences relevant for the benefit assessment
Morbidity	↑	Advantages in the endpoint pulmonary exacerbations and hospitalisation for pulmonary exacerbations as well as in the domains of the CFQ-R respiratory system and weight problems
Health-related quality of life	↑	Advantages in all domains of the CFQ-R in the quality of life category
Side effects	↔	No differences relevant for the benefit assessment
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		

Mortality

Study VX17-445-102 Endpoint category Endpoint	IVA/TEZ/ELX + IVA + BSC	Placebo + BSC	IVA/TEZ/ELX + IVA + BSC vs Placebo + BSC
Mortality			
No deaths occurred			

[1] Data from the dossier assessment of the G-BA (published on 1 December 2020) as well as from the amendment unless indicated otherwise.

Morbidity

Study VX17-445-102 Endpoint category Endpoint	IVA/TEZ/ELX + IVA + BSC			Placebo + BSC			IVA/TEZ/ ELX + IVA + BSC vs Placebo + BSC
	N	Number Events n	Persons with at least one event, n (%)	N	Number Events n	Persons with at least one event, n (%)	Rate ratio[3)] [95% CI]; p value
Morbidity							
Pulmonary exacerbations[1)]							
Pulmonary exacerbations	200	41	31 (15.5)	203	113	76 (37.4)	0.37 [0.25; 0.55]; < 0.0001
Hospitalisations because of pulmonary exacerbation	200	9	7 (3.5)	203	32	27 (13.3)	0.29 [0.14, 0.61]; 0.0010

Study VX17-445-102 Endpoint category Endpoint	IVA/TEZ/ELX + IVA + BSC				Placebo + BSC				IVA/TEZ/ ELX + IVA + BSC vs Placebo + BSC
	Baseline		Absolute Change at Week 24		Baseline		Absolute Change at Week 24		MD[6)] [95% CI]; p value; Hedges' g [95% CI]
	N	MV (SD)	N	MV (SD)	N	MV (SD)	N	MV (SD)	
Morbidity									
Symptomatology – Cystic Fibrosis Questionnaire-Revised (CFQ-R)[1)]									
FEV1%									
FEV1 (absolute change)	200	61.6 (15.0)	196	13.9 (0.6)	203	61.3 (15.5)	203	−0.4 (0.5)	14.3 [12.7; 15.8]; < 0.0001
Sweat chloride concentration [mmol/l] (presented additionally)									
Sweat chloride (absolute change)	199	102.30 (11.85)	199	−42.19 (0.92)	201	102.93 (9.78)	201	−0.35 (0.92)	−41.84 [−44.40; −39.28]; < 0.0001

Study VX17-445-102 Endpoint category Endpoint	IVA/TEZ/ELX + IVA + BSC				Placebo + BSC				IVA/TEZ/ ELX + IVA + BSC vs Placebo + BSC
	Baseline		Absolute Change at Week 24		Baseline		Absolute Change at Week 24		MD[6] [95% CI]; p value; Hedges' g [95% CI]
	N	MV (SD)	N	MV (SD)	N	MV (SD)	N	MV (SD)	
Body mass index (BMI)[1]									
BMI ([kg/m²] absolute change)	200	21.49 (3.07)	198	1.13 (0.07)	203	21.31 (3.14)	202	0.09 (0.07)	1.04 [0.85; 1.23]; < 0.0001
BMI (z-score, absolute change[m])	71	−0.37 (0.79)	64	0.34 (0.05)	74	−0.40 (0.98)	68	0.04 (0.05)	0.30 [0.17; 0.43]; < 0.0001

Study VX17-445-102 Endpoint category Endpoint	IVA/TEZ/ELX + IVA + BSC			Placebo + BSC			IVA/TEZ/ ELX + IVA + BSC vs Placebo + BSC
	N	MV (SD)	Number of responders, n (%)	N	MV (SD)	Number of responders, n (%)	RR [95% CI]; p value[4]
Morbidity							
Symptomatology – Cystic Fibrosis Questionnaire-Revised (CFQ-R([1), 5), 16]							
Respiratory system	200	68.28 (16.91)	103 (51.5)	203	69.98 (17.76)	14 (6.9)	7.55 [4.48; 12.72]; < 0.0001
Gastro-intestinal symptoms	200	83.06 (18.1)	29 (14.5)	203	83.36 (16.89)	25 (12.32)	1.17 [0.71; 1.92]; 0.5349
Weight problems[9]	185	74.41 (30.99)	62 (33.51)	179	74.12 (31.71)	32 (17.88)	1.91 [1.31; 2.77]; 0.0007

Health-related quality of life

Study VX17-445-102 Endpoint category Endpoint	IVA/TEZ/ELX + IVA + BSC			Placebo + BSC			IVA/TEZ/ ELX + IVA + BSC vs Placebo + BSC
	N	MV (SD)	Number of responders, n (%)	N	MV (SD)	Number of responders, n (%)	RR [95% CI]; p value[4)]
Health-related quality of life							
Symptomatology – Cystic Fibrosis Questionnaire-Revised (CFQ-R)[1), 5), 16)]							
Physical well-being	200	76.5 (21.7)	51 (25.50)	203	76.4 (21.6)	12 (5.91)	4.38 [2.42; 7.94]; < 0.0001
Emotional state	200	82.05 (16.0)	22 (11.0)	203	80.2 (16.7)	8 (3.94)	2.77 [1.27; 6.07]; 0.0108
Vitality[9)]	185	62.8 (17.1)	46 (24.86)	179	63.8 (18.3)	6 (3.35)	7.51 [3.30; 17.07]; < 0.0001
Social limitations	203	70.5 (17.0)	34 (17.0)	200	68.8 (17.9)	10 (4.93)	3.48 [1.77; 6.83]; 0.0003
Role functioning[9)]	185	81.7 (17.5)	30 (16.22)	179	83.3 (15.2)	7 (3.91)	4.17 [1.88; 9.23]; 0.0004
Body image	200	78.8 (22.1)	34 (17.0)	203	77.2 (23.5)	18 (8.87)	1.91 [1.12; 3.26]; 0.0179
Eating disorders	200	90.0 (17.9)	22 (11.0)	203	89.1 (17.5)	11 (5.42)	2.06 [1.03; 4.10]; 0.0398
Therapy stress	200	59.2 (19.2)	33 (16.5)	203	61.4 (20.2)	9 (4.43)	3.72 [1.83; 7.57]; 0.0003
Subjective health assessment[9)]	185	63.5 (20.5)	77 (41.62)	179	64.2 (20.1)	10 (5.59)	7.45 [4.01; 13.98]; < 0.0001

Side effects[10), 11)]

Study VX17-445-102 Endpoint category Endpoint	IVA/TEZ/ELX + IVA + BSC		Placebo + BSC		IVA/TEZ/ELX + IVA + BSC vs Placebo + BSC
	N	Patients with event n (%)	N	Patients with event n (%)	RR[12)] [95% CI]; p value
Side effects					
AE	202	187 (92.6)	201	187 (93.0)	–[13)]
AE grade ≥ 3 or 4	202	19 (9.4)	201	9 (4.5)	2.10 [0.97; 4.53]; 0.058[14)]
SAE	202	20 (9.9)	201	16 (8.0)	1.24 [0.66; 2.33]; 0.496[14)]
AE that led to discontinuation of study medication	202	2 (1.0)	201	0	4.98 [0.24; 102.99]c; 0.212[15)]

1) All randomised patients with a CFTR mutation who received ≥ 1 dose of study medication.
2) Mean difference calculated using MMRM: adjusted for baseline FEV1% (< 70 vs ≥ 70%), age at screening (< 18 vs ≥ 18 years), sex (male vs. female), treatment, round, treatment × round as fixed effects in the model.
3) Rate ratio: Negative binomial regression model with fixed treatment effect as well as continuous baseline FEV1% (< 70 vs ≥ 70%), age at screening (< 18 vs. ≥ 18 years), and sex (male vs female) as covariates.
4) Relative risk: Generalised linear model: Treatment group, baseline FEV1% (< 70 vs ≥ 70%), age at screening (< 18 vs. ≥ 18 years), and sex (male vs female) as covariates.
5) Score: 0–100; higher values correspond a lower symptomatology or better quality of life.
6) Mean difference calculated using MMRM: Data from all available rounds up to Week 24 with treatment, round, and treatment × round as fixed effects and baseline FEV1% (< 70 vs ≥ 70%), age at screening (< 18 vs ≥ 18 years), and sex (male vs female) as covariates.
7) Domain “weight problems” is not included in the questionnaire version for children.
8) Pooled version “children from 12 to 13” and “Adolescents and adults”.
9) Domain not included in the questionnaire version for children.
10) AE coded as death or with the MedDRA Preferred Term “infective exacerbations of cystic fibrosis” were not included in the analysis because these events were explicitly reported as a separate endpoint.
11) All patients who received ≥ 1 dose of study medication.
12) Effect estimator based on the data of module 4.
13) Patient relevance cannot be clearly assessed.
14) Calculation of the RR using a four-field table. Module 4 did not specify whether the RR calculation took into consideration the stratification factors – baseline FEV1% (< 70 vs ≥ 70%), age at screening (< 18 vs ≥ 18 years), and sex (male vs female) – used for randomisation.
15) Calculation taken from IQWIG benefit assessment of ivacaftor (new therapeutic indication: Cystic fibrosis, combination therapy with ivacaftor/tezacaftor/elexacaftor in patients 12 years and older (heterozygous for F508del and MF mutation))
16) Improvement by at least 15 points. Evaluations for deterioration are not available.

Abbreviations: CFTR: Cystic Fibrosis Transmembrane Conductance Regulator; FAS: full analysis set; FEV1%: Proportion of forced one-second volume to standardised normal value in percent; IVA/TEZ/ELX: ivacaftor/tezacaftor/elexacaftor; CI: confidence interval; MedDRA: Medical Dictionary for Regulatory Activities; (S)AE: (serious) adverse event(s); MMRM: Mixed model for repeated measurements; MV: mean value; n.c.: not calculable; RR: relative risk; SD: standard deviation;

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

Patients aged 12 years and older with cystic fibrosis who are heterozygous for a F508del mutation in the CFTR gene as well as a mutation with minimal function (MF) on the second allele

approx. 1000 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: 28 January 2021):

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

Treatment with ivacaftor/tezacaftor/elexacaftor may be initiated and monitored only by specialists who are experienced in the treatment of patients with cystic fibrosis.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Ivacaftor/tezacaftor/elexacaftor	€ 158,139.51
+ ivacaftor	€ 100,977.84
Total costs	€ 259,117.35
Best supportive care	different for each individual patient
Appropriate comparator therapy	
Best supportive care	different for each individual patient

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

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 18 February 2021.

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

Berlin, 18 February 2021

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken