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 (New Therapeutic Indication: Cystic Fibrosis, Combination Treatment with Ivacaftor/Tezacaftor/Elexacaftor in Patients 12 Years and Older (Homozygous for F508del Mutation))

of 18 February 2021

At its session on 18 February 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 on DD 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 in accordance with the resolution of 18 February 2021 (Federal Gazette, BAnz AT xx xx 2021):

Ivacaftor

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

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

Kalydeco tablets are indicated in a combination regimen with ivacaftor/tezacaftor/elexacaftor tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis (CF) who are homozygous for the F508del mutation in the CFTR gene or heterozygous for F508del and have a minimal function (MF) mutation in the CFTR gene.

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

Kalydeco tablets are indicated in a combination regimen with ivacaftor/tezacaftor/elexacaftor tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis (CF) who are homozygous for the F508del mutation in the CFTR gene.

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

Patients aged 12 years and older with cystic fibrosis (CF) who are homozygous for the F508del mutation in the CFTR gene

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

Lumacaftor/ivacaftor
or
Tezacaftor/ivacaftor in combination with ivacaftor

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

Indication of a major 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 differences relevant for the benefit assessment.
Morbidity	↑↑	Advantages in the endpoints pulmonary exacerbations as well as the domains respiratory system and weight problems of the CFQ-R
Health-related quality of life	↑↑	Advantages in the domains of physical well-being, vitality, role functioning, burden of therapy, and subjective health assessment of the CFQ-R
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		

Study VX18-445-109 (parallel, double-blind RCT over 24 weeks): Ivacaftor/tezacaftor/elexacaftor + ivacaftor (IVA/TEZ/ELX + IVA) vs tezacaftor/ivacaftor + ivacaftor (TEZ/IVA + IVA)

Mortality

Study VX18-445-109 Endpoint category Endpoint	IVA/TEZ/ELX + IVA[a)]	TEZ/IVA + IVA[a)]	IVA/TEZ/ELX + IVA vs TEZ/IVA + IVA
Mortality			
No deaths occurred			

[1] Data from the dossier assessment of the IQWiG (A20-77) and from the addenda (A21-03 and G21-03) unless otherwise indicated.

Morbidity

Study VX18-445-109 Endpoint category Endpoint	IVA/TEZ/ELX + IVA[a]		TEZ/IVA + IVA[a]		IVA/TEZ/ELX + IVA vs TEZ/IVA + IVA
	N	Persons with event, n (%)	N	Persons with event, n (%)	RR [95% CI]; p value[b]
Morbidity					
Pulmonary exacerbations					
Pulmonary Exacerbations[c]	87	10 (11.5)	88	36 (40.9)	0.28 [0.15; 0.53]; < 0.001
Serious pulmonary exacerbations	87	1 (1.1)	88	9 (10.2)	0.11 [0.01; 0.87]; 0.010[e]
Cystic Fibrosis Questionnaire-Revised (CFQ-R)[f]					
Respiratory system	87	40 (46.0)	88	9 (10.2)	4.50 [2.32; 8.69]; < 0.001
Gastrointestinal symptoms	87	8 (9.2)	88	9 (10.2)	0.90 [0.36; 2.22]; 0.818
Weight problems	78	22 (28.2)	80	8 (10.0)	2.82 [1.34; 5.95]; 0.007

Study VX18-445-109 Endpoint category Endpoint	IVA/TEZ/ELX + IVA[a]			TEZ/IVA + IVA[a]			IVA/TEZ/ELX + IVA vs TEZ/IVA + IVA
	N[i]	Values at start of study MV (SD)	Change at Week 24 MV (SD)	N[i]	Values at start of study MV (SD)	Change at Week 24 MV (SD)	MD [95% CI]; p value[j]
Morbidity							
FEV1%							
FEV_1[k] absolute change	86	63.00 (16.72)	11.96 (8.41)[l]	87	64.21 (15.11)	1.98 (5.37)[l]	10.15 [8.18; 12.12]; < 0.001[m]
Sweat chloride concentration[c] *(presented additionally)*							
Sweat chloride – absolute change	87	89.0 (12.2)	−46.2 (1.3)	88	89.8 (11.7)	−3.4 (1.2)	−42.8 [−46.2; −39.3]; < 0.0001
Body mass index (BMI)							

Study VX18-445-109 Endpoint category Endpoint	IVA/TEZ/ELX + IVA[a)]			TEZ/IVA + IVA[a)]			IVA/TEZ/ELX + IVA vs TEZ/IVA + IVA
	N[i)]	Values at start of study MV (SD)	Change at Week 24 MV (SD)	N[i)]	Values at start of study MV (SD)	Change at Week 24 MV (SD)	MD [95% CI]; p value[j)]
Absolute change in BMI	61	21.17 (3.43)	1.70 (1.38)	62	21.92 (3.89)	0.15 (0.78)	1.44 [1.07; 1.82]; < 0.001[n)]
BMI (age dependent z-score)[o)]	19	−0.79 (0.98)	0.52 (0.47)	16	−0.33 (0.95)	−0.01 (0.48)	0.51 [0.20; 0.82]; 0.002[n)]

Health-related quality of life

Study VX18-445-109 Endpoint category Endpoint	IVA/TEZ/ELX + IVA[a)]		TEZ/IVA + IVA[a)]		IVA/TEZ/ELX + IVA vs TEZ/IVA + IVA
	N	Persons with event, n (%)	N	Persons with event, n (%)	RR [95% CI]; p value[b)]
Health-related quality of life					
Cystic Fibrosis Questionnaire-Revised (CFQ-R)[f)]					
Physical well-being	87	24 (27.6)	88	7 (8.0)	3.47 [1.58; 7.63] 0.002
Emotional state	87	8 (9.2)	88	6 (6.8)	1.35 [0.49; 3.73]; 0.564
Vitality[g)]	78	25 (32.1)	80	13 (16.3)	1.97 [1.09; 3.57]; 0.025
Social limitations	87	10 (11.5)	88	3 (3.4)	3.37 [0.96; 11.84]; 0.058
Role functioning[g)]	78	16 (20.5)	80	5 (6.3)	3.28 [1.26; 8.52]; 0.015
Body image	87	11 (12.6)	88	8 (9.1)	1.39 [0.59; 3.29]; 0.453
Eating disorders	87	11 (12.6)	88	5 (5.7)	2.23 [0.81; 6.14]; 0.122
Burden of therapy	87	19 (21.8)	88	8 (9.1)	2.40 [1.11; 5.19]; 0.026
Subjective health assessment[g)]	78	26 (33.3)	80	8 (10.0)	3.33 [1.61; 6.91]; 0.001

Side effects

Study VX18-445-109 Endpoint category Endpoint	IVA/TEZ/ELX + IVA[a)]		TEZ/IVA + IVA[a)]		IVA/TEZ/ELX + IVA vs TEZ/IVA + IVA
	N	Patients with event, n (%)	N	Patients with event n (%)	RR [95% CI]; p value[b)]
Side effects[k)]					
AE (presented additionally)[h)]	87	77 (88.5)	88	75 (85.2)	-
AE CTCAE Grade ≥ 3[c)]	87	6 (6.9)	88	4 (4.5)	1.52 [0.44; 5.19]; 0.507
SAEs[h)]	87	4 (4.6)	88	6 (6.8)	0.67 [0.20; 2.31]; 0.558[d]
Discontinuation because of AE[h)]	87	1 (1.1)	88	2 (2.3)	0.51 [0.05; 5.48]; 0.682[d]
Skin and subcutaneous tissue disorders (SOC, AE)	87	20 (23.0)	88	4 (4.5)	5.06 [1.80; 14.19]; < 0.001[d]

a) The treatment was carried out against a background of basic medication.
b) Evaluation of the CFQ-R by generalised linear model (GLM) using the binomial distribution and a log-link function.
c) Calculation taken from G-BA benefit assessment of ivacaftor/tezacaftor/elexacaftor (exceeding the € 50 million limit, cystic fibrosis, combination treatment with ivacaftor in patients aged 12 years and older (homozygous for F508del mutation)) published on 1 December 2020.
d) surveyed via the SAEs as “Infectious pulmonary exacerbation of cystic fibrosis” (PT).
e) Own calculation, unconditional exact test (CSZ method according to [14]).
f) Pooled version “Children from 12 to 13 years” and “Adolescents and adults”; improvement defined as an increase in CFQ-R score of at least 15 points compared with baseline; it is unclear whether this improvement was at one survey time point during the 24-week study period or at multiple survey time points.
g) Domain for adolescents or adults; not intended for children [12 to 13 years].
h) Without recording of PT “Infectious pulmonary exacerbation of cystic fibrosis”.
i) Number of patients who were included in the evaluation according to the data provided by the pharmaceutical company. However, for the BMI and the age-dependent BMI evaluation, these are presumably patients for whom values were available at least at the start of study and Week 24; the estimation of the parameters of the MMRM models could be based on higher patient numbers. At least the values at the start of study are based on 28 vs 30 patients for the age-dependent BMI evaluation (presumably the patients who were ≤ 20 years at screening) and 87 vs 88 patients for the BMI. Overall, for the age-dependent BMI evaluation, it is unclear whether ≥ 70% of patients contribute to the estimation of the parameters of the MMRM model.
j) MMRM; dependent variable is absolute change from baseline; adjusted for age (< 18 vs ≥ 18 years at screening), baseline FEV1%, and use of a CFTR modulator at screening; additionally treatment, study time, and treatment×study time as fixed effects in the model.
k) The values at the start of study are based on 87 vs 88 patients; the values at the change at Week 24 are based on 52 vs 53 patients.
l) Higher values mean better symptomatology; a positive group difference means an advantage for ivacaftor + ivacaftor/tezacaftor/elexacaftor.
m) Effect represents the difference between treatment groups of the adjusted mean difference of absolute changes over 24 weeks. Week 15 is excluded.
n) Effect represents the difference between treatment groups of changes from the start of study to Week 24.
o) According to information provided by the pharmaceutical company in Module 4 B, only for patients ≤ 20 years of age; the weight surveys required for this purpose after screening were planned for patients ≤ 21 years of age.

Abbreviations: CFQ-R: Cystic Fibrosis Questionnaire Revised; ELEXA: elexacaftor; CI: confidence interval; IVA: Ivacaftor; n: number of patients with (at least 1) event; N: number of patients evaluated; PT: preferred term; RCT: randomised controlled trial; RR: relative risk; SOC: system organ class; SAE: serious adverse event; TEZA: tezacaftor; AE: adverse event

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

Patients aged 12 years and older with cystic fibrosis who are homozygous for the F508del mutation

approx. 2400 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 Kalydeco (active ingredient: ivacaftor) at the following publicly accessible link (last access: 9 February 2021):

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

Treatment with ivacaftor 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	€ 100,977.84
+ ivacaftor/tezacaftor/elexacaftor	€ 158,139.51
Total costs	€ 259,117.35
Appropriate comparator therapy:	
Tezacaftor/ivacaftor	€ 78,708.73
+ ivacaftor	€ 100,977.84
Total costs:	€ 179,686.57
or	
Lumacaftor/ivacaftor	€ 148,415.91

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