Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee 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 (Exceeding the € 50 Million Limit: Cystic Fibrosis, Combination Regimen with Tezacaftor/Ivacaftor in Patients over 12 Years of Age (Heterozygous with Respect to F508del))

of 20 February 2020

At its session on 20 February 2020, 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 last 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 as follows:

Courtesy translation – only the German version is legally binding.

Ivacaftor

Resolution of: 20 February 2020
Entry into force on: 20 February 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 10 October 2018):

Kalydeco tablets are also indicated in a combination regimen with tezacaftor 100 mg/ivacaftor 150 mg tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis (CF) who are heterozygous for the F508del mutation and have one of the following mutations in the CFTR gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G and 3849+10kbC→T.

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

Patients 12 years of age and older with cystic fibrosis who are heterozygous for the F508del mutation and who display one of the following mutations in the CFTR gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G and 3849+10kbC→T.

Appropriate comparator therapy:

- 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 (especially antibiotics for pulmonary infections, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy (in the sense of the HeilmittelRichtlinie (Remedies Directive)), making full use of all possible dietary measures).

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

An additional benefit is not proven.

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Study results according to endpoints:[1]

Patients 12 years of age and older with cystic fibrosis who are heterozygous for the F508del mutation and who display one of the following mutations in the CFTR gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G and 3849+10kbC→T.

Study VX14-661-108: Ivacaftor + tezacaftor/ivacaftor (IVA + TEZ/IVA) + BSC vs placebo + BSC (RCT; 8 weeks; cross-over design)

Study VX14-661-108 **Endpoint category** **Endpoint**	**IVA + TEZ/IVA + BSC**	**Placebo + BSC**	**IVA + TEZ/IVA + BSC vs placebo + BSC**
Mortality			
No deaths occurred.			

Study VX14-661-108 **Endpoint category** **Endpoint**	**IVA + TEZ/IVA + BSC**			**Placebo + BSC**			**IVA + TEZ/IVA + BSC vs placebo + BSC**
	N[a)]	**Values at start of study MV (SD)**	**Change at the end of study MV (SD)**	**N[a)]**	**Values at start of study MV (SD)**	**Change at the end of study MV (SD)**	**MD[b)] [95% CI]; p value**
Morbidity							
FEV_1[c)]							
absolute change in FEV_1%	159	62.15 (14.74)	6.69 (7.03)	160	62.22 (14.28)	−0.37 (6,58)	6.67 [5.49; 7.84]; < 0.001
Body Mass Index (BMI)							
BMI ([kg/m²] absolute change)	158	24.06 (4.74)	0.34 (0.96)	160	24.63 (5,41)	0.18 (0.81)	0.15 [−0.00; 0.31]; 0.052

Study VX-661-108 **Endpoint category** **Endpoint**	**IVA + TEZ/IVA + BSC**		**Placebo + BSC**		**IVA + TEZ/IVA + BSC vs placebo + BSC**
	N[a)]	**Number of events n_E (n_E/patient years)[d), e)]**	**N[a)]**	**Number of events n_E (n_E/patient years)[d), e)]**	**Rate ratio [95% CI]; p value**
Morbidity					
Pulmonary exacerbations	161	11 (0.39)	161	20 (0.71)	0.53 [0.26; 1.12]; 0.096
Hospitalisation because of pulmonary exacerbations	161	3 (0.11)	161	5 (0.18)	0.79 [0.19; 3.23]; 0.737

[1] Data from the dossier evaluation of the IQWiG (A19-71) unless otherwise indicated.

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Study VX-661-108 Endpoint category Endpoint	IVA + TEZ/IVA + BSC			Placebo + BSC			IVA + TEZ/IVA + BSC vs placebo + BSC
	N[a)]	Values at start of study MV (SD)	Change at the end of study MV (SD)	N[a)]	Values at start of study MV (SD)	Change at the end of study MV (SD)	MD[b)] [95% CI]; p value
Morbidity							
Symptomatology – Cystic Fibrosis Questionnaire-Revised (CFQ-R) [f), g)]							
Respiratory system	161	68.20 (17.51)	9.82 (16.79)	160	68.75 (18.29)	−2.35 (17.29)	10.82 [8.30; 13.33]; < 0.001 Hedges' g: 0.84 [0.61; 1.07]
Age							
< 18 years	21	81.22 (11.38)	3.44 (13.23)	24	82.29 (14.37)	−2.17 (15.67)	1.78 [−3.38; 6.94]; 0.472
≥ 18 years	140	66.25 (17.47)	10.78 (17.09)	136	66.37 (17.91)	−2.38 (17.61)	12.30 [9.58; 15.03]; < 0.001 Hedges' g: 0.95 [0.70; 1.20]
Total interaction							0.004
Gastrointestinal symptoms	161	84.20 (16.51)	−0.64 (14.35)	160	83.57 (17.13)	2.11 (12.17)	−2.57 [−4.77; −0.36]; 0.023 Hedges' g: −0.24 [−0.46; −0.02]
Weight problems[h)]	155	87.10 (24.73)	4.10 (21.60)	155	87.82 (21.78)	−0.43 (18.27)	3.58 [0.42; 6.74]; 0.026 Hedges' g: 0.245 [0.02; 0.47]

Study VX14-661-108 Endpoint category Endpoint	IVA + TEZ/IVA + BSC			Placebo + BSC			IVA + TEZ/IVA + BSC vs placebo + BSC
	N	Values at start of study MV (SD)	Change at the end of study MV (SD)	N	Values at start of study MV (SD)	Change at the end of study MV (SD)	MD [95% CI]; p value
Morbidity							
Sweat chloride concentration (additionally shown)[2]							
Absolute change [mmol/l]	158	66.99 (26.81)	59.97 (29.03)	157	70.12 (25.73)	71.72 (25.25)	−9.287 [−11.824; −6.751]; < 0.0001

Study VX14-661-108 Endpoint	IVA + TEZ/IVA + BSC	Placebo + BSC	IVA + TEZ/IVA + BSC vs placebo + BSC

[2] Data from the dossier

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category Endpoint	N[a)]	Values at start of study MV (SD)	Change at the end of study MV (SD)	N[a)]	Values at start of study MV (SD)	Change at the end of study MV (SD)	MD[b)] [95% CI]; p value
Health-related quality of life							
Cystic Fibrosis Questionnaire-Revised (CFQ-R)[f), g)]							
Physical well-being	161	73.30 (22.31)	3.25 (18.38)	160	70.21 (23.01)	−4.29 (17.67)	6.76 [4.01; 9.50]; < 0.001 Hedges' g: 0.49 [0.26; 0.71]
Emotional state	161	82.00 (15.78)	1.16 (10.68)	160	80.23 (15.93)	−0.44 (12.21)	2.51 [0.84; 4.19]; 0.004 Hedges' g: 0.28 [0.06; 0.50]
Vitality[h)]	155	60.54 (17.72)	4.03 (19.31)	155	59.24 (19.91)	−4.27 (18.92)	7.86 [5.20; 10.53]; < 0.001 Hedges' g: 0.57 [0.34; 0.79]
Social limitations	161	69.93 (17.65)	3.62 (12.46)	161	67.42 (18.32)	−0.43 (11.82)	2.80 [1.04; 4.57]; 0.002 Hedges' g: 0.29 [0.07; 0.51]
Role function[h)]	155	83.92 (16.56)	0.48 (14.35)	155	82.98 (16.23)	−3.79 (14.82)	3.14 [0.81; 5.47]; 0.009 Hedges' g: 0.26 [0.04; 0.49]
Body image	161	82.88 (17.30)	4.14 (12.84)	161	84.13 (18.03)	−0.35 (12.61)	2.17 [0.48; 3.85]; 0.006 Hedges' g: 0.22 [0.00; 0.44]
Eating disorders	161	93.03 (14.48)	−0.62 (13.68)	160	93.37 (12.93)	−2.80 (13.17)	1.42 [−0.55; 3.38]; 0.156
Therapy stress	161	63.98 (21.79)	3.31 (15.66)	161	62.73 (21.78)	−1.22 (15.19)	2.86 [0.85; 4.87]; 0.007 Hedges' g: 0.24 [0.02; 0.46]
Subjective perception of health[h)]	155	65.95 (20.56)	5.59 (15.11)	156	63.89 (21.37)	−3.01 (15.11)	8.93 [6.69; 11.16]; < 0.001 Hedges' g: 0.74 [0.51; 0.97]
Age							
< 18 years	15	67.41 (21.19)	5.19 (10.17)	19	73.68 (21.34)	1.85 (17.15)	−0.94 [−9.02; 7.14]; 0.804
≥ 18 years	140	65.79 (20.56)	5.63 (15.57)	137	62.53 (21.09)	−3.65 (14.77)	10.28 [8.00; 12.56]; < 0.001 Hedges' g: 0.86 [0.62; 1.11]
Total interaction							0.002
SF-12-v2[i)]							
Physical	160	49.99	1.21	158	49.64	−1.28	2.40 [1.47; 3.33];

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Study VX14-661-108 Endpoint category Endpoint	IVA + TEZ/IVA + BSC			Placebo + BSC			IVA + TEZ/IVA + BSC vs placebo + BSC
	N	Values at start of study MV (SD)	Change at the end of study MV (SD)	N	Values at start of study MV (SD)	Change at the end of study MV (SD)	MD [95% CI]; p value
component score (PCS)[j]		(7.78)	(6.49)		(7.21)	(6.18)	< 0.001 Hedges' g: 0.50 [0.27; 0.72]
Age							
< 18 years	21	53.27 (4.75)	0.57 (3.51)	23	53.86 (4.64)	0.30 (3.92)	−0.29 [−1.25; 0.67]; 0.518
≥ 18 years	139	49.49 (8.04)	1.31 (6.83)	135	48.92 (7.34)	−1.55 (6.46)	2.91 [1.86; 3.95]; < 0.001 Hedges' g: 0.58 [0.34; 0.83]
Total interaction							0.009
Mental Component Score (MCS)[j]	160	52.55 (7.09)	0.22 (6.53)	158	51.56 (8.98)	−0.77 (8.08)	1.35 [0.31; 2.38]; 0.011 Hedges' g: 0.25 [0.03; 0.47]

Study VX14-661-108 Endpoint category Endpoint	IVA + TEZ/IVA + BSC		Placebo + BSC		IVA + TEZ/IVA + BSC vs placebo + BSC
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI] p value
Side effects					
AEs (additionally shown)	162	117 (72.2)	162	126 (77.8)	–
SAEs[k] [3]	162	4 (2.5)	162	9 (5.6)	0.44 [0.12; 1.54]; 0.26
Discontinuation because of AEs	162	0 (0.0)	162	1 (0.6)	–[l]

a) Number of patients included in the evaluation to calculate the effect estimation. Values at the start of study may be based on different patient numbers. Patients from all 6 treatment sequences are included in the evaluation with the value from the respective treatment period.
b) MMRM: Effect represents the difference between the treatment groups in the changes averaged over the course of the study between the respective measurement time and the start of study.
c) Primary endpoint of the Study VX14-661-108
d) Negative binomial model in a generalised linear mixed model. Fixed effects are treatment, period, and FEV_1 at baseline, patient as random effect; log(study time) as offset.
e) Event rate (nE/patient years) is calculated by dividing the total number of events by the total number of years (sum of the observation time of all patients included in the analysis)
f) Higher values mean a better health-related quality of life or symptomatology
g) Domains on symptomatology, children [12 to 13 years] and adolescents or adults – pooled
h) Domain for adolescents or adults; not intended for children [12 to 13 years].
i) Higher values mean a better quality of life or symptomatology; a positive group difference corresponds to an advantage for ivacaftor

[3] Data from the addendum (A20-06) of the IQWiG

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j) Data are available for two of the eight sub-scales. Because data is not available for all sub-scales, the two existing sub-scales are not displayed.
k) Without surveying the PT “infectious pulmonary exacerbations”
l) Not reasonably calculable

Abbreviations
BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire-Revised; FEV_1: forced expiratory volume in 1 second; IVA: Ivacaftor; CI: confidence interval; MD: Mean difference; MMRM: mixed model with repeated measurements; MV: mean value; n: number of patients with (at least 1) event; n_E: number of events; N: number of patients evaluated; PT: preferred term RCT: randomised controlled trial; RR: relative risk; SD: standard deviation; SF-12-v2: 12-Item Short Form Health Survey Version 2; SAE: serious adverse event; TEZ: tezacaftor; AE: adverse event; vs: versus

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	∅	No suitable data were submitted for the benefit assessment.
Morbidity	∅	No suitable data were submitted for the benefit assessment.
Health-related quality of life	∅	No suitable data were submitted for the benefit assessment.
Side effects	∅	No suitable data were submitted for the benefit assessment.

Explanations:
↑, ↓: statistically significant and relevant positive or negative effect with high or unclear risk of bias
↑↑, ↓↓: statistically significant and relevant positive or negative effect with low risk of bias
↔: no relevant difference
∅: no data available
n.a.: not assessable

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

Patients 12 years of age and older with cystic fibrosis who are heterozygous for the F508del mutation and who display one of the following mutations in the CFTR gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G and 3849+10kbC→T.

approx. 200-300 patients

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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: 5 February 2020):

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

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

4. Treatment costs

Annual treatment costs:

Patients 12 years of age and older with cystic fibrosis who are heterozygous for the F508del mutation and who display one of the following mutations in the CFTR gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G and 3849+10kbC→T.

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Ivacaftor	€ 100,977.84
Tezacaftor/ivacaftor	€ 78,708.73
Total	€ 179,686.57
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 2020

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 20 February 2020.

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

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Berlin, 20 February 2020

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

Prof. Hecken

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