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 (Homozygous 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:

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 homozygous for the F508del mutation.

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

Patients older than 12 years of age with cystic fibrosis and who are homozygous for the F508del mutation.

Appropriate comparator therapy:

Lumacaftor/ivacaftor

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

An additional benefit is not proven.

Study results according to endpoints:[1]

Patients older than 12 years of age with cystic fibrosis and who are homozygous for the F508del mutation.

Indirect comparison: Ivacaftor + tezacaftor/ivacaftor (IVA + TEZ/IVA; RCT VX14-661-106, 24 weeks) vs lumacaftor/ivacaftor (LUM/IVA; RCTs VX12-809-103 and VX12-809-104, 24 weeks) via the bridge comparator placebo:

Endpoint category Endpoint Comparison Study	IVA + TEZ/IVA[a] or LUM/IVA[a]		Placebo[a]		Group difference
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Mortality					
Overall mortality					
IVA + TEZ/IVA vs placebo					
VX14-661-106	251	0 (0)	258	0 (0)	–
LUM/IVA vs placebo					
VX12-809-103	182	0 (0)	184	0 (0)	–
VX12-809-104	187	0 (0)	186	0 (0)	–

Endpoint category Endpoint Comparison Study	IVA + TEZ/IVA[a] or LUM/IVA[a]			Placebo[a]			Group difference
	N[b]	Values at start of study MV (SD)	Change at the end of study MV (SD)	N[b]	Values at start of study MV (SD)	Change at the end of study MV (SD)	MD [95% CI]; p value[c]
Morbidity							
FEV_1 (absolute change) %[d]							
IVA + TEZ/IVA vs placebo							
VX14-661-106	226	59.65 (14.69)	3.60 (7.17)	237	60.35 (15.65)	−1.47 (6.38)	4.79 [3.58; 6.00]; < 0.001[e]
LUM/IVA vs placebo							
VX12-809-103	166	60.48 (14.29)	1.58 (7.60)	173	60.45 (13.22)	−0.67 (6.95)	2.41 [0.84; 3.97]; 0.003[e]
VX12-809-104	173	60.59 (14.01)	2.53 (7.54)	177	60.37 (14.32)	−0.25 (7.10)	2.67 [1.13; 4.20]; < 0.001
Total[f]							2.54 [1.45; 3.63]; < 0.001
Indirect comparison via bridge comparators[g]:							
IVA + TEZ/IVA vs LUM/IVA							2.25 [0.62; 3.88]; 0.007[h]
Body Mass Index (BMI)							
BMI ([kg/m²] absolute change)							
IVA + TEZ/IVA vs placebo							

[1] Data from the dossier evaluation of the IQWiG (A19-70) unless otherwise indicated.

Endpoint category Endpoint Comparison Study	IVA + TEZ/IVA[a] or LUM/IVA[a] N[b]	Values at start of study MV (SD)	Change at the end of study MV (SD)	Placebo[a] N[b]	Values at start of study MV (SD)	Change at the end of study MV (SD)	Group difference MD [95% CI]; p value[c]
VX14-661-106	237	20.96 (2.95)	0.19 (0.82)	245	21.12 (2.88)	0.12 (0.70)	0.06 [−0.08; 0.19]; 0.413[e]
LUM/IVA vs placebo							
VX12-809-103	176	21.68 (3.17)	0.29 (1.08)	184	21.03 (2.96)	0.19 (0.98)	0.14 [−0.07; 0.34]; 0.191[e]
VX12-809-104	180	21.32 (2.89)	0.40 (0.88)	183	21.02 (2.89)	0.05 (0.95)	0.36 [0.17; 0.54]; < 0.001[e]
Total[f]							0.26 [0.12; 0.40]; < 0.001
Indirect comparison via bridge comparators[g]:							
IVA + TEZ/IVA vs LUM/IVA							−0.21 [−0.40; −0.01]; 0.037[h]
BMI (age-dependent z-score, absolute change[i])							
IVA + TEZ/IVA vs placebo							
VX14-661-106	76	−0.58 (0.95)	−0.06 (0.04)	74	−0.37 (0.83)	−0.02 (0.04)	−0.04 [−0.15; 0.07]; 0.471[e]
LUM/IVA vs placebo							
VX12-809-103	58	−0.36 (0.81)	0.10 (0.37)	69	−0.59 (0.98)	0.04 (0.52)	0.08 [−0.06; 0.22]; 0.271[e]
VX12-809-104	58	−0.33 (0.90)	0.15 (0.31)	53	−0.50 (0.89)	−0.05 (0.38)	0.22 [0.10; 0.35]; < 0.001[e]
Total[j]							0.16 [0.06; 0.25]; < 0.001
Indirect comparison via bridge comparators[k]:							
IVA + TEZ/IVA vs LUM/IVA							−0.20 [−0.34; −0.05]; 0.007

Endpoint category Endpoint Comparison Study	IVA + TEZ/IVA[a] or LUM/IVA[a]		Placebo[a]		Group difference
	N	Number of events (n_E/patient years)[l]	N	Number of events (n_E/patient years)[l]	Rate ratio [95% CI]; p value[m]
Morbidity					
Pulmonary exacerbations					
IVA + TEZ/IVA vs placebo					
VX14-661-106	248	78 (0.69)	256	122 (1.05)	0.65 [0.48; 0.88]; 0.005
LUM/IVA vs placebo					
VX12-809-103	182	73 (0.89)	184	112 (1.31)	0.66 [0.48; 0.92]; 0.014
VX12-809-104	187	79 (0.93)	187	139 (1.62)	0.57 [0.42; 0.77]; < 0.001
Total					0.61 [0.49; 0.76]; < 0.001[j]
Indirect comparison via bridge comparators[k]:					
IVA + TEZ/IVA vs LUM/IVA					1.06 [0.73; 1.55]; 0.760
Hospitalisation because of pulmonary exacerbations					
IVA + TEZ/IVA vs placebo					
VX14-661-106	248	26 (0.23)	256	33 (0.28)	0.78 [0.44; 1.36]; 0.380
LUM/IVA vs placebo					
VX12-809-103	182	17 (0.21)	184	46 (0.54)	0.38 [0.22, 0.66]; < 0.001
VX12-809-104	187	23 (0.27)	187	59 (0.69)	0.39 [0.24; 0.64]; < 0.001
Total					0.38 [0.27; 0.56]; < 0.001[j]
Indirect comparison via bridge comparators[k]:					
IVA + TEZ/IVA vs LUM/IVA					2.02 [1.03; 3.95]; 0.040

Endpoint category Endpoint Domain Comparison Study	IVA + TEZ/IVA[a] or LUM/IVA[a]			Placebo[a]			Group difference
	N[b]	Values at start of study MV (SD)	Change at the end of study MV (SD)	N[b]	Values at start of study MV (SD)	Change at the end of study MV (SD)	MD [95% CI]; p value
Morbidity							
Symptomatology – Cystic Fibrosis Questionnaire-Revised (CFQ-R) [n), o)]							
Respiratory system							
IVA + TEZ/IVA vs placebo							
VX14-661-106	246	70.06 (16.81)	4.11 (15.88)	256	69.92 (16.64)	−1.36 (16.60)	5,11 [3.20; 7.02]; < 0.001[c]
LUM/IVA vs placebo							
VX12-809-103	172	69.29 (17.42)	1.60 (16.92)	184	70.54 (16.03)	−0.50 (15.89)	1.51 [−1.58; 4.61]; 0.355[c]
VX12-809-104	179	67.36	3.51	185	67.05	0.71	2.85 [−0.38; 6.08];

Endpoint category Endpoint Domain Comparison Study	IVA + TEZ/IVA[a] or LUM/IVA[a] N[b]	Values at start of study MV (SD)	Change at the end of study MV (SD)	Placebo[a] N[b]	Values at start of study MV (SD)	Change at the end of study MV (SD)	Group difference MD [95% CI]; p value
		(18.54)	(18.76)		(18.39)	(17.06)	0.098[c]
Total							2.15 [−0.08; 4.38]; 0.058
Indirect comparison via bridge comparators[g]:							
IVA + TEZ/IVA vs LUM/IVA							2.96 [0.03; 5.89] 0.048[p] Hedges' g: 0.29 [0.06; 0.52][k]
Gastrointestinal symptoms							
IVA + TEZ/IVA vs placebo							
VX14-661-106	246	82.03 (16.22)	−0.52 (18.30)	256	80.47 (19.07)	0.82 (16.48)	−0.10 [−1.93; 1.72]; 0.911[c]
LUM/IVA vs placebo							
VX12-809-103	171	81.97 (16.07)	−0.23 (16.58)	184	83.95 (16.62)	−0.18 (16.23)	−1.05 [−4.20; 2.09]; 0.511[c]
VX12-809-104	179	82.83 (19.28)	−1.18 (15.04)	185	82.25 (19.22)	0.60 (18.41)	−1.65 [−4.72; 1.43]; 0.293[c]
Total[q]							Hedges' g: −0.09 [−0.23; 0.06]; 0.252
Indirect comparison via bridge comparators[r]:							
IVA + TEZ/IVA vs LUM/IVA							Hedges' g: 0.08 [−0.15; 0.30]; 0.514[p]
Weight problems[s]							
IVA + TEZ/IVA vs placebo							
VX14-661-106	223	74.52 (32.47)	2.34 (27.59)	231	76.01 (30.77)	−1.22 (24.34)	0.51 [−2.89; 3.90]; 0.770[c]
LUM/IVA vs placebo							
VX12-809-103	158	77.85 (33.49)	0.21 (28.02)	165	73.94 (33.56)	1.62 (27.74)	−0.50 [−5.69; 4.69]; 0.850[c]
VX12-809-104	166	73.88 (34.21)	3.62 (28.43)	166	74.80 (32.33)	−1.60 (27.65)	4.86 [−0.47; 10.19]; 0.074[c]
Total[q]							Hedges' g: 0.08 [−0.07; 0.23]; 0.292
Indirect comparison via bridge comparators[r]:							

Endpoint category Endpoint Domain Comparison Study	IVA + TEZ/IVA[a] or LUM/IVA[a] N[b]	IVA + TEZ/IVA[a] or LUM/IVA[a] Values at start of study MV (SD)	IVA + TEZ/IVA[a] or LUM/IVA[a] Change at the end of study MV (SD)	Placebo[a] N[b]	Placebo[a] Values at start of study MV (SD)	Placebo[a] Change at the end of study MV (SD)	Group difference MD [95% CI]; p value
IVA + TEZ/IVA vs LUM/IVA							Hedges' g: −0.06 [−0.30; 0.18]; 0.623[p]

Endpoint category Endpoint Domain Comparison Study	IVA + TEZ/IVA[a] or LUM/IVA[a] N[b]	IVA + TEZ/IVA[a] or LUM/IVA[a] Values at start of study MV (SD)	IVA + TEZ/IVA[a] or LUM/IVA[a] Change at the end of study MV (SD)	Placebo[a] N[b]	Placebo[a] Values at start of study MV (SD)	Placebo[a] Change at the end of study MV (SD)	Group difference MD [95% CI]; p value
Health-related quality of life							
Cystic Fibrosis Questionnaire-Revised (CFQ-R)[n),o)]							
Physical well-being							
IVA + TEZ/IVA vs placebo							
VX14-661-106	246	77.56 (20.94)	2.01 (16.50)	256	78.23 (21.71)	−1.08 (14.78)	3.85 [1.88; 5.82]; < 0.001[c]
LUM/IVA vs placebo							
VX12-809-103	171	79.03 (19.33)	−0.97 (17.83)	184	80.70 (19.23)	−2,21 (15.67)	0.80 [−2.59; 4.18]; 0.644[c]
VX12-809-104	180	78.90 (19.75)	0.54 (19.14)	184	78.77 (21.01)	−3.89 (18.32)	4.28 [0.63; 7.93]; 0.022[c]
Total[q]							Hedges' g 0.14 [−0.01; 0.29]; 0.064
Indirect comparison via bridge comparators[r]:							
IVA + TEZ/IVA vs LUM/IVA							Hedges' g: 0.17 [−0.06; 0.40]; 0.146[p]
Emotional state							
IVA + TEZ/IVA vs placebo							
VX14-661-106	246	82.61 (15.73)	−0.02 (12.01)	256	81.90 (16.18)	−0.37 (13.61)	0.59 [−1.02; 2.21]; 0.471[c]
LUM/IVA vs placebo							
VX12-809-103	171	81.32 (16.09)	1.46 (13.41)	184	81.33 (15.02)	0.59 (11.89)	0.79 [−1.59; 3.17]; 0.514[c]
VX12-809-104	180	90.25 (10.41)	1.97 (12.97)	184	83.91 (16.17)	−1.16 (11.30)	3.21 [0.88; 5.54]; 0.007[c]
Total[q]							Hedges' g: 0.17 [0.02; 0.32]; 0.024
Indirect comparison via bridge comparators[r]:							

Endpoint category Endpoint Domain Comparison Study	IVA + TEZ/IVA[a] or LUM/IVA[a] N[b]	Values at start of study MV (SD)	Change at the end of study MV (SD)	Placebo[a] N[b]	Values at start of study MV (SD)	Change at the end of study MV (SD)	Group difference MD [95% CI]; p value
IVA + TEZ/IVA vs LUM/IVA							Hedges' g: −0.11 [−0.34; 0.12]; 0.343[p]
Vitality[s]							
IVA + TEZ/IVA vs placebo							
VX14-661-106	223	64.58 (18.59)	−0.61 (18.38)	231	62.25 (17.92)	−1.22 (15.85)	2.30 [0.10; 4.49]; 0.040[c]
LUM/IVA vs placebo							
VX12-809-103	157	64.78 (17.55)	−1.17 (16.81)	166	64.56 (16.48)	−2.39 (15.69)	1.04 [−2.37; 4.45]; 0.550[c]
VX12-809-104	167	63.62 (18.05)	0.70 (18.75)	165	62.70 (17.09)	−1.88 (16.85)	2.86 [−0.68; 6.39]; 0.113[c]
Total[q]							Hedges' g: 0.11 [−0.04; 0.26]; 0.155
Indirect comparison via bridge comparators[r]:							
IVA + TEZ/IVA vs LUM/IVA							Hedges' g: 0.05 [−0.19; 0.29]; 0.694[p]
Social limitations							
IVA + TEZ/IVA vs placebo							
VX14-661-106	246	72.06 (16.85)	0.82 (12.24)	256	73.93 (16.32)	−1.06 (12.21)	1.52 [0.03; 3.01]; 0.045[c]
LUM/IVA vs placebo							
VX12-809-103	173	74.02 (16.54)	−1.74 (12.72)	184	73.29 (17.17)	−1.44 (13.45)	−0.30 [−2.86; 2.27]; 0.821[c]
VX12-809-104	180	74.46 (16.42)	−1.40 (14.50)	185	73.27 (16.71)	−2.68 (13.64)	1.40 [−1.28; 4.08]; 0.306[c]
Total[q]							Hedges' g: 0.04 [−0.10; 0.18]; 0.587
Indirect comparison via bridge comparators[r]:							
IVA + TEZ/IVA vs LUM/IVA							0.12 [−0.10; 0.35]; 0.288[p]
Role function[s]							
IVA + TEZ/IVA vs placebo							
VX14-661-106	223	83.93 (17.02)	1.73 (14.04)	230	84.02 (16.79)	0.31 (14.15)	1.53 [−0.31; 3.37]; 0.103[c]
LUM/IVA vs placebo							
VX12-809-103	157	82.72 (16.35)	0.69 (13.28)	166	84.74 (17.50)	−1.81 (14.06)	2.16 [−0.72; 5.04]; 0.140[c]
VX12-809-104	166	83.86 (15.70)	0.72 (17.63)	166	84.03 (17.76)	−2.55 (15.96)	3.08 [−0.29; 6.44]; 0.073[c]

Endpoint category Endpoint Domain Comparison Study	IVA + TEZ/IVA[a] or LUM/IVA[a] N[b]	IVA + TEZ/IVA[a] or LUM/IVA[a] Values at start of study MV (SD)	IVA + TEZ/IVA[a] or LUM/IVA[a] Change at the end of study MV (SD)	Placebo[a] N[b]	Placebo[a] Values at start of study MV (SD)	Placebo[a] Change at the end of study MV (SD)	Group difference MD [95% CI]; p value
Total[q]							Hedges' g: 0.17 [0.01; 0.32]; 0.034
Indirect comparison via bridge comparators[r]:							
IVA + TEZ/IVA vs LUM/IVA							Hedges' g: −0.04 [−0.28; 0.20]; 0.756[p]
Body image							
IVA + TEZ/IVA vs placebo							
VX14-661-106	246	76.30 (22.09)	0.05 (14.80)	256	77.47 (23.15)	1.68 (14.70)	−0.51 [−2.31; 1.29]; 0.577[c]
LUM/IVA vs placebo							
VX12-809-103	173	77.91 (21.89)	2.05 (16.97)	184	76.94 (22.66)	2.90 (16.89)	−0.56 [−3.75; 2.64]; 0.732[c]
VX12-809-104	180	78.29 (21.07)	1.51 (15.39)	185	77.13 (22.47)	−0.30 (18.83)	2.10 [−1.18; 5.38]; 0.209[c]
Total[q]							Hedges' g: 0.05 [−0.09; 0.19]; 0.498
Indirect comparison via bridge comparators[r]:							
IVA + TEZ/IVA vs LUM/IVA							Hedges' g: −0.10 [−0.32; 0.13]; 0.406[p]
Eating disorders							
IVA + TEZ/IVA vs placebo							
VX14-661-106	246	89.74 (17.34)	−0.63 (13.64)	256	91.15 (17.06)	−0.84 (12.73)	1.05 [−0.59; 2.70]; 0.209[c]
LUM/IVA vs placebo							
VX12-809-103	172	90.89 (15.70)	0.36 (15.66)	183	92.58 (15.20)	−1.03 (12.02)	0.90 [−1.67; 3.47]; 0.492[c]
VX12-809-104	180	93.02 (13.89)	−1.67 (14.11)	185	91.27 (16.40)	−2.94 (16.34)	1.69 [−1.28; 4.65]; 0.263[c]
Total[q]							Hedges' g: 0.09 [−0.06; 0.24]; 0.225
Indirect comparison via bridge comparators[r]:							
IVA + TEZ/IVA vs LUM/IVA							Hedges' g: 0.01 [−0.22; 0.24]; 0.911[p]
Burden of therapy							
IVA + TEZ/IVA vs placebo							
VX14-661-106	246	60.53 (19.69)	2.88 (13.77)	256	62.11 (20.02)	−0.68 (13.03)	3.37 [1.65; 5.10]; < 0.001[c]
LUM/IVA vs placebo							

Endpoint category Endpoint Domain Comparison Study	IVA + TEZ/IVA[a] or LUM/IVA[a]			Placebo[a]			Group difference
	N[b]	Values at start of study MV (SD)	Change at the end of study MV (SD)	N[b]	Values at start of study MV (SD)	Change at the end of study MV (SD)	MD [95% CI]; p value
VX12-809-103	173	57.73 (19.90)	3.43 (13.53)	184	57.86 (18.02)	2.29 (14.03)	1.12 [−1.58; 3.81]; 0.416[c]
VX12-809-104	180	57.87 (21.25)	2.56 (18.28)	185	57.11 (20.15)	3.09 (17.84)	−0.19 [−3.48; 3.10]; 0.909[c]
Total[q]							Hedges' g: 0.03 [−0.11; 0.18]; 0.649
Indirect comparison via bridge comparators[r]:							
IVA + TEZ/IVA vs LUM/IVA							Hedges' g: 0.28 [0.05; 0.51]; 0.018[p]
Subjective perception of health[s]							
IVA + TEZ/IVA vs placebo							
VX14-661-106	223	64.35 (21.36)	1.82 (15.66)	231	64.90 (20.33)	−2.60 (17.35)	3.20 [1.15; 5.24]; 0.002[c]
LUM/IVA vs placebo							
VX12-809-103	159	64.59 (20.79)	1.12 (18.62)	166	69.36 (19.70)	−2.68 (15.52)	2.32 [−1.19; 5.83]; 0.195[c]
VX12-809-104	167	66.00 (20.49)	0.67 (16.95)	166	65.49 (20.79)	−1.67 (15.78)	2.40 [−0.84; 5.63]; 0.146[c]
Total[q]							Hedges' g: 0.14 [−0.02; 0.29] 0.081
Indirect comparison via bridge comparators[r]:							
IVA + TEZ/IVA vs LUM/IVA							Hedges' g: 0.10 [−0.14; 0.34]; 0.404[p]

Endpoint category Endpoint Comparison Study	IVA + TEZ/IVA[a] or LUM/IVA[a]		Placebo[a]		Group difference
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Side effects					
AEs (additionally shown)					
IVA + TEZ/IVA vs placebo					
VX14-661-106	251	227 (90.4)	258	245 (95.0)	–
LUM/IVA vs placebo					
VX12-809-103	182	174 (95.6)	184	174 (94.6)	–
VX12-809-104	187	177 (94.7)	186	181 (97.3)	–
SAEs[2, t]					

[2] Data from the addendum (A20-05) of the IQWiG

Endpoint category Endpoint Comparison Study	IVA + TEZ/IVA[a)] or LUM/IVA[a)]		Placebo[a)]		Group difference
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
IVA + TEZ/IVA vs placebo					
VX14-661-106	251	14 (5.6)	258	26 (10.1)	0.55 [0.30; 1.04]; 0.064[t)]
LUM/IVA vs placebo					
VX12-809-103	182	19 (10.4)	184	15 (8.2)	1.28 [0.67; 2.44]; 0.453[t)]
VX12-809-104	187	10 (5.3)	186	17 (9.1)	0.59 [0.28; 1.24]; 0.164[t)]
Total[f)]					0.92 [0.56; 1.50]; 0.738
Indirect comparison via bridge comparators[g)]: **IVA + TEZ/IVA vs LUM/IVA**					-[u)]
Discontinuation because of AEs[3]					
IVA + TEZ/IVA vs placebo					
VX14-661-106	251	No data available	258	8 (3.1)	0.77 [0.27; 2.19]; 0.625
LUM/IVA vs placebo					
VX12-809-103	182	6 (3.3)	184	4 (2.2)	1.52 [0.44; 5.28]; 0.513
VX12-809-104	187	No data available	186	2 (1.1)	no data available
Total[f)]					2.38 [0.84; 6.78]; 0.083
Indirect comparison via bridge comparators[g)]: **IVA + TEZ/IVA vs LUM/IVA**					-[v)]
Rash (PT, AE)					
IVA + TEZ/IVA vs placebo					
VX14-661-106	251	4 (1.6)	258	13 (5.0)	0.32 [0.10; 0.96]; 0.032[w)]
LUM/IVA vs placebo					
VX12-809-103	182	7 (3.8)	184	2 (1.1)	3.54 [0.75; 16.81]; 0.097[w)]
VX12-809-104	187	18 (9.6)	186	5 (2.7)	3.58 [1.36; 9.44]; 0.005[w)]
Total[x)]					3.57 [1.57; 8.13]; 0.002
Indirect comparison via bridge comparators[k)]: **IVA + TEZ/IVA vs LUM/IVA**					0.09 [0.02; 0.35]; < 0.001

a) The treatment took place against the background of a symptomatic concomitant therapy.
b) Number of patients considered in the evaluation to calculate the effect estimate; the values at the start of study may be based on more patients and the values at the end of study on fewer patients.
c) 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.
d) Primary endpoint of the Studies VX14-661-106, VX-809-103, and VX-809-104
e) Calculated according to MMRM model, see benefit assessment
f) Model with fixed effects
g) Indirect comparison according to Bucher
h) Calculation of the IQWiG; assuming asymptotic normal distribution

Endpoint category Endpoint Comparison Study	IVA + TEZ/IVA[a)] or LUM/IVA[a)]		Placebo[a)]		Group difference
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value

i) Only for patients < 20 years
j) Calculation by the IQWiG from meta-analysis, model with fixed effect, inverse variance method.
k) Calculation of the IQWiG; indirect comparison according to Bucher
l) Calculation of the IQWiG; the event rate (n_E/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)
m) Negative binomial model with treatment, sex, age group at the start of study (< 18 years vs ≥ 18 years), and FEV_1 at the start of study as covariates
n) Higher values mean a better health-related quality of life or symptomatology
o) Domains on symptomatology, children [12 to 13 years] and adolescents or adults – pooled
p) p value calculation of the IQWiG, assuming asymptotic normal distribution
q) Meta-analysis with fixed effect using the effect measure Hedges' g; no information on MD
r) Indirect comparison according to Bucher using the effect measure Hedges' g; no information on MD
s) Domain for adolescents or adults; not intended for children [12 to 13 years].
t) without surveying the PT "infectious pulmonary exacerbations"
u) No presentation of effect estimates because on the intervention side of the indirect comparison, there is only one study with endpoint-specific high risk of bias.
v) No usable data
w) Calculation by the IQWiG, unconditional exact test (CSZ method)
x) Own calculation, meta-analysis, model with fixed effect, Mantel-Haenszel method

Abbreviations:
BMI: Body Mass Index; CFQ-R: Cystic Fibrosis Questionnaire-Revised; FEV_1: forced expiratory volume in 1 second; IVA: ivacaftor; CI: confidence interval; LUM: lumacaftor; MD: mean difference; MedDRA: Medical Dictionary for Regulatory Activities; MMRM: mixed model with repeated measurements; MV: mean value; N: number of patients evaluated; n: number of patients with (at least 1) event; n_E: number of events; PT: preferred term RCT: randomised controlled trial; RR: relative risk; SD: standard deviation; SAE: serious adverse event; TEZ: tezacaftor; AE: adverse event; vs: versus

Summary of results for clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No differences relevant for the benefit assessment.
Morbidity	↔	No differences relevant for the benefit assessment.
Health-related quality of life	↔	No differences relevant for the benefit assessment.
Side effects	↔	No differences relevant 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 older than 12 years of age with cystic fibrosis and 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: 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 older than 12 years of age with cystic fibrosis and who are homozygous for the F508del mutation.

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
Appropriate comparator therapy:	
Lumacaftor/ivacaftor	€ 148,415.91

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.

Berlin, 20 February 2020

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

Prof. Hecken