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 Tezacaftor/Ivacaftor (Reassessment of an Orphan Drug after the € 50 Million Turnover Limit Was Exceeded: Cystic Fibrosis, Combination Regimen with Ivacaftor in Patients over 12 Years of Age (Homozygous with Respect to F508del))

of 17 December 2020

At its session on 17 December 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 will be amended as follows:

1. The information relating to tezacaftor/ivacaftor as amended by the resolution of 16 May 2019 (Federal Gazette, BAnz AT 6 June 2019 B2) is hereby repealed.

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

Tezacaftor/ivacaftor

Resolution of: 17 December 2020
Entry into force on: 17 December 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 31 October 2018):

Symkevi is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who are heterozygous for the F508del mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (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.

Therapeutic indication of the resolution (resolution of 17 December 2020):

Symkevi is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of patients with cystic fibrosis (CF) aged 12 years and older 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 tezacaftor/ivacaftor in combination with 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.

[1] Data from the dossier assessment of the IQWiG (A20-54) unless otherwise indicated.

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	↔	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 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

Indirect comparison: Tezacaftor/ivacaftor + ivacaftor (TEZ/IVA + 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**	**TEZ/IVA + 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					
TEZ/IVA + 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**	**TEZ/IVA + 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							
FEV_1 (absolute change) %[c]							
TEZ/IVA + 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
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
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							2.54 [1.45; 3.63]; < 0.001
Indirect comparison via bridge comparators[d]:							
TEZ/IVA + IVA vs LUM/IVA							2.25 [0.62; 3.88]; 0.007[e]
Body Mass Index (BMI)							
BMI ([kg/m²] absolute change)							
TEZ/IVA + IVA vs placebo							
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
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

Endpoint category Endpoint Comparison Study	TEZ/IVA + 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
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
Total							0.26 [0.12; 0.40]; < 0.001
Indirect comparison via bridge comparators[d]:							
TEZ/IVA + IVA vs LUM/IVA							−0.21 [−0.40; −0.01]; 0.037[e]
BMI (age-dependent z-score, absolute change[f])							
TEZ/IVA + 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
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
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
Overall[e]							0.16 [0.06; 0.25]; < 0.001
Indirect comparison via bridge comparators[g]:							
TEZ/IVA + IVA vs LUM/IVA							−0.20 [−0.34; −0.05]; 0.007

Endpoint category Endpoint Comparison Study	TEZ/IVA + IVA [a)] or LUM/IVA[a)]		Placebo[a)]		Group difference
	N	Number of events (n_E/patient years)[h)]	N	Number of events (n_E/patient years)[h)]	Rate ratio [95% CI]; p value
Morbidity					
Pulmonary exacerbations					
TEZ/IVA + 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
Indirect comparison via bridge comparators[g)]:					
TEZ/IVA + IVA vs LUM/IVA					1.06 [0.73; 1.55]; 0.760
Hospitalisation because of pulmonary exacerbations					
TEZ/IVA + 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
Indirect comparison via bridge comparators[g)]:					
TEZ/IVA + IVA vs LUM/IVA					2.02 [1.03; 3.95]; 0.040

Endpoint category Endpoint Domain Comparison Study	TEZ/IVA + IVA [a)] or LUM/IVA[a)]			Placebo[a)]			Group difference
	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							
Symptomatology – Cystic Fibrosis Questionnaire-Revised (CFQ-R)[i),j)]							
Respiratory system							
TEZ/IVA + 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
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

Endpoint category Endpoint Domain Comparison Study	N	TEZ/IVA + IVA [a)] or LUM/IVA[a)] Values at start of study MV (SD)	Change at the end of study MV (SD)	N	Placebo[a)] Values at start of study MV (SD)	Change at the end of study MV (SD)	Group difference MD [95% CI]; p value
VX12-809-104	179	67.36 (18.54)	3.51 (18.76)	185	67.05 (18.39)	0.71 (17.06)	2.85 [−0.38; 6.08]; 0.098
Total							2.15 [−0.08; 4.38]; 0.058
Indirect comparison via bridge comparators[d)]:							
TEZ/IVA + IVA vs LUM/IVA							2.96 [0.03; 5.89] 0.048[e)] Hedges' g: 0.29 [0.06; 0.52][g)]
Gastrointestinal symptoms							
TEZ/IVA + 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
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
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
Overall[k)]							Hedges' g: −0.09 [−0.23; 0.06]; 0.252
Indirect comparison via bridge comparators[l)]:							
TEZ/IVA + IVA vs LUM/IVA							Hedges' g: 0.08 [−0.15; 0.30]; 0.514[e)]
Weight problems[m)]							
TEZ/IVA + 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
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
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
Overall[k)]							Hedges' g: 0.08 [−0.07; 0.23]; 0.292
Indirect comparison via bridge comparators[l)]:							

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

Endpoint category Endpoint Domain Comparison Study	N	TEZ/IVA + IVA [a)] or LUM/IVA[a)] Values at start of study MV (SD)	Change at the end of study MV (SD)	N	Placebo[a)] Values at start of study MV (SD)	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)[i),j)]							
Physical well-being							
TEZ/IVA + 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
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
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
Overall[k)]							Hedges' g: 0.14 [−0.01; 0.29]; 0.064
Indirect comparison via bridge comparators[l)]:							
TEZ/IVA + IVA vs LUM/IVA							Hedges' g: 0.17 [−0.06; 0.40]; 0.146[e)]
Emotional state							
TEZ/IVA + 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
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
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
Overall[k)]							Hedges' g: 0.17 [0.02; 0.32]; 0.024
Indirect comparison via bridge comparators[l)]:							

Endpoint category Endpoint Domain Comparison Study	N	TEZ/IVA + IVA [a)] or LUM/IVA[a)] Values at start of study MV (SD)	Change at the end of study MV (SD)	N	Placebo[a)] Values at start of study MV (SD)	Change at the end of study MV (SD)	Group difference MD [95% CI]; p value
TEZ/IVA + IVA vs LUM/IVA							Hedges' g: −0.11 [−0.34; 0.12]; 0.343[e)]
Vitality[m)]							
TEZ/IVA + 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
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
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
Overall[k)]							Hedges' g: 0.11 [−0.04; 0.26]; 0.155
Indirect comparison via bridge comparators[l)]:							
TEZ/IVA + IVA vs LUM/IVA							Hedges' g: 0.05 [−0.19; 0.29]; 0.694[e)]
Social limitations							
TEZ/IVA + 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
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
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
Overall[k)]							Hedges' g: 0.04 [−0.10; 0.18]; 0.587
Indirect comparison via bridge comparators[l)]:							
TEZ/IVA + IVA vs LUM/IVA							0.12 [−0.10; 0.35]; 0.288[e)]
Role functioning[m)]							
TEZ/IVA + 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
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

Endpoint category Endpoint Domain Comparison Study	TEZ/IVA + IVA [a)] or LUM/IVA[a)] N	Values at start of study MV (SD)	Change at the end of study MV (SD)	Placebo[a)] N	Values at start of study MV (SD)	Change at the end of study MV (SD)	Group difference MD [95% CI]; p value
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
Overall[k)]							Hedges' g: 0.17 [0.01; 0.32]; 0.034
Indirect comparison via bridge comparators[l)]:							
TEZ/IVA + IVA vs LUM/IVA							Hedges' g: −0.04 [−0.28; 0.20]; 0.756[e)]
Body image							
TEZ/IVA + 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
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
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
Overall[k)]							Hedges' g: 0.05 [−0.09; 0.19]; 0.498
Indirect comparison via bridge comparators[l)]:							
TEZ/IVA + IVA vs LUM/IVA							Hedges' g: −0.10 [−0.32; 0.13]; 0.406[e)]
Eating disorders							
TEZ/IVA + 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
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
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
Overall[k)]							Hedges' g: 0.09 [−0.06; 0.24]; 0.225
Indirect comparison via bridge comparators[l)]:							
TEZ/IVA + IVA vs LUM/IVA							Hedges' g: 0.01 [−0.22; 0.24]; 0.911[e)]
Burden of therapy							
TEZ/IVA + IVA vs placebo							

Endpoint category Endpoint Domain Comparison Study	TEZ/IVA + IVA [a)] or LUM/IVA[a)] N	Values at start of study MV (SD)	Change at the end of study MV (SD)	Placebo[a)] N	Values at start of study MV (SD)	Change at the end of study MV (SD)	Group difference MD [95% CI]; p value
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
LUM/IVA vs placebo							
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
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
Overall[k)]							Hedges' g: 0.03 [−0.11; 0.18]; 0.649
Indirect comparison via bridge comparators[l)]:							
TEZ/IVA + IVA vs LUM/IVA							Hedges' g: 0.28 [0.05; 0.51]; 0.018[e)]
Subjective perception of health[m)]							
TEZ/IVA + 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
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
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
Overall[k)]							Hedges' g: 0.14 [−0.02; 0.29]; 0.081
Indirect comparison via bridge comparators[l)]:							
TEZ/IVA + IVA vs LUM/IVA							Hedges' g: 0.10 [−0.14; 0.34]; 0.404[e)]

Endpoint category Endpoint Comparison Study	TEZ/IVA + IVA [a)] or LUM/IVA[a)] N	Patients with event n (%)	Placebo[a)] N	Patients with event n (%)	Group difference RR [95% CI]; p value
Side effects					
AEs[n)] (presented additionally)					
TEZ/IVA + IVA vs placebo					
VX14-661-106	251	222 (88.5)	258	242 (93.8)	–
LUM/IVA vs placebo					
VX12-809-103	182	171 (94.0)	184	167 (90.8)	–
VX12-809-104	187	173 (92.5)	186	175 (94.1)	–

Endpoint category Endpoint Comparison Study	TEZ/IVA + 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
SAEs [n]					
TEZ/IVA + IVA vs placebo					
VX14-661-106	251	14 (5.6)	258	26 (10.1)	0.55 [0.30;1.04];0.064
LUM/IVA vs placebo					
VX12-809-103	182	19 (10.4)	184	15 (8.2)	1.28 [0.67; 2.44]; 0.453
VX12-809-104	187	10 (5.3)	186	17 (9.1)	0.59 [0.28; 1.24]; 0.164
Total					0.92 [0.56; 1.50]; 0.738
Indirect comparison via bridge comparators[d]: TEZ/IVA + IVA vs LUM/IVA					-[o]
Discontinuation because of AEs					
TEZ/IVA + IVA vs placebo					
VX14-661-106	251	7 (2.8)	258	8 (3.1)	0.90 [0.33; 2.44]; 0.835
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	11 (5.9)	186	2 (1.1)	5.47 [1.23; 24.34]; 0.026
Total					2.57 [0.99; 6.70]; 0.053
Indirect comparison via bridge comparators[d]: TEZ/IVA + IVA vs LUM/IVA					_[o]
Rash (PT, AE)					
TEZ/IVA + IVA vs placebo					
VX14-661-106	251	4 (1.6)	258	13 (5.0)	0.32 [0.10; 0.96]; 0.032[e]
LUM/IVA vs placebo					
VX12-809-103	182	7 (3.8)	184	2 (1.1)	3.54 [0.75; 16.81]; 0.097[e]
VX12-809-104	187	18 (9.6)	186	5 (2.7)	3.58 [1.36; 9.44]; 0.005[e]
Total					3.57 [1.57; 8.13]; 0.002
Indirect comparison via bridge comparators[d]: TEZ/IVA + 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) Primary endpoint of the Studies VX14-661-106, VX12-809-103, and VX12-809-104
d) Indirect comparison according to Bucher
e) Calculation of the IQWiG
f) Only for patients < 20 years
g) Calculation of the IQWiG; indirect comparison according to Bucher

Endpoint category Endpoint Comparison Study	TEZ/IVA + 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

h) 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)
i) Higher values mean a better health-related quality of life or symptomatology; a positive group difference means an advantage for tezacaftor/ivacaftor
j) Domains on symptomatology, children [12 to 13 years] and adolescents or adults – pooled
k) Meta-analysis with fixed effect using the effect measure Hedges' g; no information on MD
l) Indirect comparison according to Bucher using the effect measure Hedges' g; no information on MD
m) Domain for adolescents or adults; not intended for children [12 to 13 years]
n) Without surveying the PT "infectious pulmonary exacerbations"
o) 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

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; 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

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. 2,400 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 Symkevi (active ingredient combination: tezacaftor/ivacaftor) at the following publicly accessible link (last access: 28 October 2020): https://www.ema.europa.eu/documents/product-information/symkevi-epar-product-information_de.pdf

Treatment with tezacaftor/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:

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:	
Tezacaftor/ivacaftor	€ 76,603.85
Ivacaftor	€ 98,277.75
Total	€ 174,881.60
Appropriate comparator therapy:	
Lumacaftor/ivacaftor	€ 144,447.32

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 December 2020

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 17 December 2020.

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

Berlin, 17 December 2020

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

Prof. Hecken