Gemeinsamer Bundesausschuss

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 (Heterozygous with Respect to F508del))

Resolution of: 17 December 2020 Valid until: unlimited
Entry into force on: 17 December 2020
Federal Gazette, BAnz AT 12 02 2021 B4

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 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.

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 Heilmittel-Richtlinie (Remedies Directive)), making full use of all possible dietary measures).

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

An additional benefit is not proven.

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.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	n.a.	No relevant data are available.
Morbidity	n.a.	No relevant data are available.
Health-related quality of life	n.a.	No relevant data are available.
Side effects	n.a.	No relevant data are available.
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 VX14-661-108: Tezacaftor/ivacaftor + ivacaftor (TEZ/IVA + IVA) + BSC vs placebo + BSC (RCT; 8 weeks; cross-over-design)

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

[1] Data from the dossier assessment of the IQWiG (A20-55) unless otherwise indicated.

Study VX14-661-108 Endpoint category Endpoint	TEZ/IVA + IVA + BSC			Placebo + BSC			TEZ/IVA + 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 [95% CI]; p value
Morbidity							
FEV $_1$[b)]							
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/m^2] 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	TEZ/IVA + IVA + BSC		Placebo + BSC		TEZ/IVA + IVA + BSC vs placebo + BSC
	N[a)]	Number of events n$_E$ (n$_E$/patient years)[c)]	N[a)]	Number of events n$_E$ (n$_E$/patient years)[c)]	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

Study VX-661-108 Endpoint category Endpoint	TEZ/IVA + IVA + BSC			Placebo + BSC			TEZ/IVA + 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 [95% CI]; p value
Morbidity							
Symptomatology – Cystic Fibrosis Questionnaire-Revised (CFQ-R) [d), e)]							
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];

Study VX-661-108 Endpoint category Endpoint	TEZ/IVA + IVA + BSC			Placebo + BSC			TEZ/IVA + 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 [95% CI]; p value
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[f)]	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	TEZ/IVA + IVA + BSC			Placebo + BSC			TEZ/IVA + 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 (presented additionally)[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
Health-related quality of life							
Cystic Fibrosis Questionnaire-Revised (CFQ-R)[d), e)]							
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[f)]	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

[2] Data from the dossier

Study VX14-661-108 Endpoint category Endpoint	TEZ/IVA + IVA + BSC			Placebo + BSC			TEZ/IVA + 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
							Hedges' g: 0.29 [0.07; 0.51]
Role functioning[f)]	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[f)]	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[g)]							
Physical component score (PCS)[h)]	160	49.99 (7.78)	1.21 (6.49)	158	49.64 (7.21)	−1.28 (6.18)	2.40 [1.47; 3.33]; < 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

Study VX14-661-108 Endpoint category Endpoint	TEZ/IVA + IVA + BSC			Placebo + BSC			TEZ/IVA + 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
Mental component score (MCS)[h)]	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	TEZ/IVA + IVA + BSC		Placebo + BSC		TEZ/IVA + 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 (presented additionally)[i)]	162	111 (68.5)	162	122 (75.3)	–
SAEs[i)]	162	4 (2.5)	162	9 (5.6)	0.44 [0.14; 1.42]; 0.169
Discontinuation because of AEs	162	0 (0.0)	162	1 (0.6)	–[j)]

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) Primary endpoint of the Study VX14-661-108
c) Calculation of the IQWiG; 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)
d) Higher values mean a better health-related quality of life or symptomatology
e) Domains on symptomatology, children [12 to 13 years] and adolescents or adults – pooled
f) Domain for adolescents or adults; not intended for children [12 to 13 years]
g) Higher values mean a better quality of life or symptomatology; a positive group difference corresponds to an advantage for tezacaftor/ivacaftor
h) 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.
i) Without surveying the PT "infectious pulmonary exacerbations"
j) 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; 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

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

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 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:	
Tezacaftor/ivacaftor	€ 76,603.85
Ivacaftor	€ 98,277.75
Total	174,881.60
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 December 2020

Costs for additionally required SHI services: not applicable.