Gemeinsamer Bundesausschuss

Ivacaftor (Exceeding the € 50 Million Limit: Cystic Fibrosis, Patients from 6 Years of Age, Various Gating Mutations)

Resolution of: 20 February 2020 valid until: unlimited
Entry into force on: 20 February 2020
Federal Gazette, BAnz AT 26 03 2020 B3

Therapeutic indication (according to the product information of April 2019):

"Kalydeco tablets are indicated for the treatment of adults, adolescents, and children aged 6 years and older and weighing 25 kg or more with cystic fibrosis (CF) who have one of the following gating (class III) mutations in the *CFTR* gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R (see Sections 4.4 and 5.1)."

The present resolution relates exclusively to the therapeutic indication of cystic fibrosis in patients aged 6 years and older with a body weight of at least 25 kg bearing one of the following gating mutations in the CFTR gene: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R (non-G551D-mutation).

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

Patients aged 6 years and older with cystic fibrosis who have one of the following gating (class III) mutations in the *CFTR* gene G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R

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 compared with best supportive care:

Hint for a non-quantifiable additional benefit.

Study results according to endpoints:[1]

Patients aged 6 years and older with cystic fibrosis who have one of the following gating (class III) mutations in the *CFTR* gene G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R

Study VX12-770-111: Ivacaftor + BSC vs placebo + BSC (RCT; 8 weeks; cross-over design)

Endpoint category Endpoint	Ivacaftor + BSC		Placebo + BSC		Group difference
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value
Mortality					
No deaths occurred					

Endpoint category Endpoint	Ivacaftor + BSC		Placebo + BSC		Group difference
	N[a]	Number of events n_E (n_E/patient years)[b]	N[a]	Number of events n_E (n_E/patient years)[b]	Rate ratio [95% CI]; p value[c]
Morbidity					
Pulmonary exacerbations					
Children, adolescents, and adults [12 years and older].					
	30	8 (1.20[d])	29	8 (1.25[d])	0.84 [0.30; 2.36]; 0.740
Children [6 to 11 years]					
	8	2 (1.30[d])	8	2 (1.22[d])	no data available[e]
Hospitalisation because of pulmonary exacerbations					
Children, adolescents, and adults [12 years and older].					
	30	1 (0.15[d])	29	4 (0.62[d])	no data available[e]
Children [6 to 11 years]					
	8	1 (0.65[d])	8	1 (0.61[d])	no data available[e]

a: Number of patients evaluated. Because of the cross-over design, patients from both treatment sequences are included in the evaluation with the value from the respective treatment period.
b: 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)
c: Negative binomal model: Treatment and treatment sequence as fixed effects; adjusted for baseline values of FEV_1 and age and log(study time) as "offset"; calculation was performed in at least five patients with event in each group
d: Calculation of the IQWiG
e: Was not calculated by the pharmaceutical company because of the low number of events
CI: confidence interval; n: number of patients with (at least one) event; N: number of patients evaluated; RCT: randomised controlled study

[1] Data from the dossier evaluation of the IQWiG (A19-66) unless otherwise indicated.

Endpoint category Endpoint	Ivacaftor + BSC			Placebo + BSC			Group difference
	N[a]	Values at start of study MV (SD)	Change at the end of study MV[b] (SD)	N[a]	Values at start of study MV (SD)	Change at the end of study MV[b] (SD)	MD [95% CI]; p value[c]
Morbidity							
FEV_1 [h]							
FEV_1 (absolute change) %[d]	38	76.37 (20.33)	8.13 (9.95)	37	79.34 (20.84)	−5.87 (7.24)	13.76 [9.94; 17.57] < 0.001
FEV_1 (relative change) %[d]	38	76.37 (20.33)	11.44 (13.10)	37	79.34 (20.84)	−6.60 (8.89)	17.73 [12.80; 22.67]; < 0.001
Cystic Fibrosis Questionnaire-Revised (CFQ-R)[d]							
CFQ-R, domains on symptomatology[d]							
Respiratory system							
Children [12 to 13 years] and adolescents or adults – pooled							
	30	70.56 (18.28)	9.10 (16.45)	29	73.56 (20.93)	−2.11 (18.57)	9.88 [4.16; 15.60]; 0.001 Hedges' g 0.88 [0.34; 1.42]
Children [6 to 11 years]							
	8	70.83 (14.77)	23.96 (13.68)	8	78.13 (20.38)	−3.13 (28.50)	11.29 [−4.25; 26.84]; 0.135
Gastrointestinal symptoms							
Children [12 to 13 years] and adolescents or adults – pooled							
	30	80.59 (17.18)	3.45 (15.74)	29	82.38 (16.13)	2.30 (8.60)	3.68 [−0.47; 7.84]; 0.081
Effect modification by Feature FEV_1 % of the standardised normal value at the start of study							
Yes	17	84.31 (16.69)	−1.31 (10.31)	18	82.72 (17.56)	3.09 (8.35)	−2.81 [−7.01; 1.40] 0.180
No	13	80.34 (18.23)	10.19 (19.80)	11	81.82 (14.29)	1.01 (9.24)	11.21 [3.83; 18.60] 0.005 Hedges' g 1.09 [0.204; 1.97]
Children [6 to 11 years]							
	8	70.83 (33.03)	8.33 (49.60)	8	83.33 (25.20)	4.17 (33.03)	−2.08 [−21.82; 17.67]; 0.811
Weight problems[e]							
Adolescents or adults, not intended for children [12 to 13 years and 6 to 11 years]							
	27	81.48 (33.76)	14.81 (28.24)	27	91.36 (17.52)	−1.23 (21.64)	4.52 [−2.68; 11.71]; 0.212
Children 6 to 11 years additionally shown parent/caretaker version							
Respiratory system	8	75.14 (15.41)	20.00 (14.14)	8	79.86 (14.83)	1.25 (14.91)	11.26 [−2.17; 24.69]; 0.084

Endpoint category Endpoint	Ivacaftor + BSC			Placebo + BSC			Group difference
	N[a]	Values at start of study MV (SD)	Change at the end of study MV[b] (SD)	N[a]	Values at start of study MV (SD)	Change at the end of study MV[b] (SD)	MD [95% CI]; p value[c]
Morbidity							
Children 6 to 11 years additionally shown parent/caretaker version							
Gastrointestinal symptoms	8	76.39 (15.07)	−1.39 (16.20)	8	79.17 (16.20)	0.00 (14.55)	2.13 [−1.30; 5.57]; 0.183
Weight problems	8	75.00 (38.83)	0.00 (0.00)	8	70.83 (37.53)	−4.17 (41.55)	1.51 [−12.79; 15.82]; 0.818
BMI (absolute change)	38	22.24 (5.19)	0.75 (0.58)	37	22.53 (5.00)	0.04 (0.70)	0.69 [0.45; 0.92]; < 0.001
BMI (age dependent z-score, absolute change)[f]	18	0.32 (1.1)	0.27 (0.24)	17	0.49 (1.08)	0.0 (0.33)	0.23 [0.07; 0.39] p = 0.006
Sweat chloride concentration (additionally shown)[i]							
Absolute change at Week 48[mmol/l]	38[k]	93.37 (18.10)	−55.82 (24.89)	37[k]	94.23 (20.58)	−5.63 (9.83)	−49.63 [−57.80; −41.47]; < 0.001
Health-related quality of life							
Cystic Fibrosis Questionnaire-Revised (CFQ-R)[d]							
Physical well-being							
Children [12 to 13 years] and adolescents or adults – pooled							
	30	75.93 (21.05)	3.83 (10.98)	29	72.37 (23.30)	4.50 (11.13)	0.57 [−3.33; 4.48]; 0.769
Children [6 to 11 years]							
	8	72.92 (29.91)	−1.39 (14.77)	8	75.00 (27.38)	−6.94 (17.25)	3.70 [−8.86; 16.27]; 0.525
Emotional state							
Children [12 to 13 years] and adolescents or adults – pooled							
	30	75.86 (19.21)	4.91 (10.59)	29	76.84 (22.42)	1.75 (13.03)	0.42 [−4.48; 5.31]; 0.863
Children [6 to 11 years]							
	8	80.21 (14.56)	8.33 (13.73)	8	78.13 (13.86)	1.56 (13.90)	1.97 [−4.52; 8.47]; 0.501
Vitality[e]							
Adolescents or adults							
	27	60.80 (18.61)	7.10 (18.16)	27	62.96 (19.66)	0.00 (14.06)	7.09 [2.40; 11.78]; 0.004 Hedges'g: 0.79 [0.24; 1.35][g]
Social limitations							
Children [12 to 13 years] and adolescents or adults – pooled							
	30	69.92 (18.22)	4.16 (12.79)	29	67.16 (19.33)	−1.75 (9.144)	1.05 [−2.78; 4.87] 0.580

Endpoint category Endpoint	Ivacaftor + BSC			Placebo + BSC			Group difference
	N[a]	Values at start of study MV (SD)	Change at the end of study MV[b] (SD)	N[a]	Values at start of study MV (SD)	Change at the end of study MV[b] (SD)	MD [95% CI]; p value[c]
Health-related quality of life							
Cystic Fibrosis Questionnaire-Revised (CFQ-R)[d]							
Social limitations							
Children [6 to 11 years]							
	8	60.71 (23.15)	1.19 (16.84)	8	66.07 (19.62)	−10.71 (17.77)	4.87 [−9.56; 19.31]; 0.447
Role function[e]							
Adolescents or adults, not intended for children [12 to 13 years and 6 to 11 years]							
	27	79.01 (16.57)	5.86 (13.83)	27	81.79 (16.51)	0.93 (12.94)	2.99 [−1.48; 7.46]; 0.183
Body image							
Children [12 to 13 years] and adolescents or adults – pooled							
	30	77.41 (23.79)	4.60 (16.40)	29	81.99 (18.88)	−1.92 (11.14)	4.00 [−1.44; 9.43]; 0.145
Children [6 to 11 years]							
	8	72.22 (28.48)	8.33 (12.94)	8	77.78 (24.49)	5.56 (18.78)	0.63 [−14.03; 15.28]; 0.924
Eating disorders							
Children [12 to 13 years] and adolescents or adults – pooled							
	30	92.22 (14.92)	3.83 (10.40)	29	92.34 (13.31)	1.53 (13.52)	2.39 [−1.13; 5.92]; 0.178
Children [6 to 11 years]							
	8	76.39 (20.09)	−1.39 (27.50)	8	70.83 (27.18)	4.17 (15.64)	−13.22 [−35.85; 9.41]; 0.204
Burden of therapy							
Children [12 to 13 years] and adolescents or adults – pooled							
	30	60.37 (24.18)	1.53 (14.46)	29	57.09 (24.44)	1.53 (13.84)	1.94 [−4.36; 8.24]; 0.535
Children [6 to 11 years]							
	8	76.39 (17.25)	0.00 (17.82)	8	63.89 (26.39)	1.39 (34.85)	0.85 [−24.62; 26.32]; 0.938
Subjective perception of health[e]							
Adolescents or adults							
	27	60.08 (21.23)	12.76 (14.02)	27	60.91 (19.58)	0.41 (11.73)	8.23 [2.82; 13.64]; 0.004 Hedges' g: 0.85 [0.29; 1.41]
Children 6 to 11 years additionally shown parent/caretaker version							
Physical well-being	8	77.78 (18.89)	8.80 (12.03)	8	86.57 (12.03)	−11.57 (16.38)	14.81 [2.24; 27.38]; 0.026 Hedges' g: 1.09 [0.02; 2.16][f]

Endpoint category Endpoint	Ivacaftor + BSC			Placebo + BSC			Group difference
	N[a]	Values at start of study MV (SD)	Change at the end of study MV[b] (SD)	N[a]	Values at start of study MV (SD)	Change at the end of study MV[b] (SD)	MD [95% CI]; p value[c]
Health-related quality of life							
Cystic Fibrosis Questionnaire-Revised (CFQ-R)[d]							
Emotional state	8	83.33 (9.43)	1.67 (9.92)	8	90.83 (7.07)	−4.17 (7.92)	2.17 [−8.26; 12.61]; 0.650
Vitality	8	69.17 (4.96)	3.33 (7.13)	8	72.50 (13.54)	−0.83 (19.33)	1.28 [−9.31; 11.87]; 0.779
Body image	8	77.78 (31.98)	−2.78 (9.85)	8	75.00 (29.55)	5.56 (14.55)	−5.56 [−13.84; 2.72]; 0.163
Eating disorders	8	81.25 (22.60)	−6.25 (12.40)	8	83.33 (19.92)	−12.50 (34.21)	−4.99 [−24.14; 14.17]; 0.530
Burden of therapy	8	70.83 (13.20)	9.72 (24.80)	8	77.78 (11.88)	0.00 (11.88)	−1.10 [−10.97; 8.77]; 0.801
Subjective perception of health	8	77.78 (17.82)	2.78 (7.86)	8	83.33 (11.88)	0.00 (13.28)	1.94 [−8.98; 12.87] 0.670
Problems at school	8	69.44 (16.53)	11.11 (22.22)	8	75.00 (15.43)	−1.39 (16.20)	3.06 [−12.74; 18.86]; 0.669

a: Number of patients included in the evaluation to calculate the effect estimation. Values at the start of study (for other times, if necessary) may be based on different patient numbers. Because of the cross-over design, patients from both treatment sequences are included in the evaluation with the value from the respective treatment period.
b: Refers to the change from the start of study at the last time of measurement.
c: MMRM: Treatment, treatment sequence, treatment period and study time as fixed effects, patient as random effect; adjusted for baseline values of age, FEV_1 and respective CFQ-R score; effect refers to the difference over all survey times after the start of study.
d: For FEV_1 as % of the standardised normal value; higher values mean a better quality of life or symptomatology; a positive group difference corresponds to an advantage for ivacaftor.
e: Domain is not included in the questionnaires for children aged 6 to 11 and for children aged 12 to 13.
f: Only for patients < 20 years
g: Calculation of the IQWiG
h: Primary endpoint of the study
i: Data from the dossier of the pharmaceutical company.
k: Values at the start of study. The values at the end of study can be based on fewer patients.

BMI: Body Mass Index; CFQ-R: Cystic Fibrosis Questionnaire-Revised; FEV_1: forced expiratory volume in 1 second; CI: confidence interval; MD: mean difference; MMRM: mixed model with repeated measurements; MV: mean value; N: number of patients evaluated; RCT: randomised controlled trial; SD: standard deviation.

Endpoint category Endpoint	Ivacaftor + BSC		Placebo + BSC		Group difference
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p value
Side effects					
AEs (additionally shown)	38	28 (73.7)	37	31 (83.8)	–
SAEs				not usable[c]	
Discontinuation because of AEs	38	0 (0)	37	0 (0)	–[b]

a: Number of patients evaluated. Because of the cross-over design, patients from both treatment sequences are included in the evaluation with the value from the respective treatment period.
b: Not reasonably calculable
c: Data are not usable because a large proportion of patients with the event of PT "cystic fibrosis of the lungs" as well as events that can be both side effects and symptomatology of the disease is included.
CI: confidence interval; n: number of patients with (at least one) event; N: number of patients evaluated; RCT: randomised controlled trial; RR: relative risk; SAE: serious adverse event; AE: adverse event.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No differences relevant for the benefit assessment taking into consideration the results in patients aged 12 years and older with a G551D mutation.
Morbidity	↑	Advantages taking into consideration the results in patients aged 12 years and older with a G551D mutation.
Health-related quality of life	↑	Advantages taking into consideration the results in patients aged 12 years and older with a G551D mutation.
Side effects	↔	No differences relevant for the benefit assessment. Data on SAE not usable, taking into consideration the results in patients aged 12 years and older with a G551D mutation.

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 aged 6 years and older with cystic fibrosis who have one of the following gating (class III) mutations in the *CFTR* gene G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R

10–11 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 aged 6 years and older with cystic fibrosis who have one of the following gating (class III) mutations in the *CFTR* gene G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Ivacaftor	€ 201,955.67
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