Gemeinsamer Bundesausschuss

Ivacaftor (Exceeding the € 50 Million Limit: Cystic Fibrosis, Patients from 18 Years of Age, R117H Mutation)

Resolution of: 20 February 2020 Valid until: unlimited
Entry into force on: 20 February 2020
Federal Gazette, BAnz AT 03 04 2020 B2

Therapeutic indication (in accordance with the product information of April 2019):

Kalydeco tablets are also indicated for the treatment of adults aged 18 years and older with cystic fibrosis (CF) who have an R117H mutation in the CFTR gene (see sections 4.4 and 5.1).

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

Patients from the age of 18 years with cystic fibrosis who have an R117H mutation in the CFTR gene

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-RL (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 minor additional benefit.

Study results according to endpoints:[1]

Patients from the age of 18 years with cystic fibrosis who have an R117H mutation in the CFTR gene

Study VX11-770-110: Ivacaftor (IVA) + BSC vs placebo + BSC (RCT; 24 weeks)

[1] Data from the dossier evaluation of the IQWiG (A19-68) unless otherwise indicated.

Study VX11-770-110 Endpoint category Endpoint	IVA + BSC	Placebo + BSC	IVA + BSC vs placebo + BSC
Mortality			
No deaths occurred.			

Study VX11-770-110 Endpoint category Endpoint	IVA + BSC			Placebo + BSC			IVA + BSC vs. placebo + BSC
	N[a]	Values at start of study MV (SD)	Change at the end of study[b] MV (SD)	N[a]	Values at start of study MV (SD)	Change at the end of study[b] MV (SD)	MD [95% CI]; p value[c]
Morbidity							
FEV_1[d]							
FEV_1% (absolute change)[e]	24	67.03 (15.37)	7.43 (6.88)	26	62.21 (14.41)	0.72 (6.10)	5.47 [1.05; 9.89]; 0.017
Body Mass Index (BMI)							
kg/m^2 (absolute change)	24	26.89 (5.23)	0.60 (0.82)	26	24.95 (5.71)	0.25 (0.74)	0.32 [−0.17; 0.80]; 0.192
Sweat chloride concentration (additionally shown)[2]							
[mmol/l] (absolute change)	23	69.34 (24.10)	−31.71 (14.42)	26	73.01 (17.32)	−10.03 (17.01)	−20.75 [−29.02; −12.48]; < 0.0001

Study VX11-770-110 Endpoint category Endpoint	IVA + BSC		IVA + BSC		IVA + BSC vs placebo + BSC
	N	Number of events n_E (n_E/patient years)[f]	N	Number of events n_E (n_E/patient years)[f]	Rate ratio [95% CI]; p value[g]
Morbidity					
Pulmonary exacerbations	24	13 (1.23[h])	26	17 (1.51[h])	0.74 [0.35; 1.56]; 0.434
Hospitalisation because of pulmonary exacerbations	24	2 (0.19[h])	26	7 (0.62[h])	0.33 [0.07; 1.61]; 0.171

Study VX11-770-110 Endpoint category Endpoint	IVA + BSC			Placebo + BSC			IVA + BSC vs. placebo + BSC
	N[a]	Values at start of study MV (SD)	Change at the end of study[b] MV (SD)	N[a]	Values at start of study MV (SD)	Change at the end of study[b] MV (SD)	MD [95% CI]; p value[i]
Morbidity							
Symptomatology (CFQ-R, domains on symptomatology)[j]							

2 Data from the dossier of the pharmaceutical company.

Respiratory system	24	68.43 (19.12)	14.66 (20.37)	26	59.19 (23.20)	−0.72 (21.27)	12.10 [4.52; 19.68]; 0.002 Hedges' g: 0.91 [0.32; 1.50]
Gastrointestinal symptoms	24	90.28 (15.48)	−2.12 (13.89)	26	83.76 (20.90)	−4.83 (11.02)	0.95 [−4.13; 6.03]; p = 0.708
Weight problems	24	93.06 (19.61)	0.00 (21.08)	26	88.46 (22.98)	−4.35 (23.15)	2.10 [−4.99; 9.20]; 0.554

Study VX11-770-110	**IVA + BSC**			**Placebo + BSC**			**IVA + BSC vs. placebo + BSC**
Endpoint category Endpoint	**N[a]**	**Values at start of study MV (SD)**	**Change at the end of study[b] MV (SD)**	**N[a]**	**Values at start of study MV (SD)**	**Change at the end of study[b] MV (SD)**	**MD [95% CI]; p value[i]**
Health-related quality of life							
CFQ-R, domains on health-related quality of life[j]							
Physical well-being	24	71.01 (27.84)	10.52 (24.67)	26	60.90 (32.96)	−3.62 (25.42)	10.42 [2.10; 18.75]; 0.015 Hedges' g: 0.71 [0.13; 1.29]
Emotional state	24	90.00 (11.96)	2.54 (9.30)	26	79.23 (21.44)	−2.61 (11.32)	6.04 [1.88; 10.20]; 0.005 Hedges' g: 0.83 [0.25; 1.42]
Pseudomonas aeruginosa infection status							
positive	14	87.62 (12.77)	4.44 (9.57)	18	76.30 (21.72)	−2.22 (13.25)	8.11 [2.48; 13.73]; 0.006 Hedges' g: 1.04 [0.28; 1.80]
negative	10	93.33 (10.42)	0.00 (8.82)	8	85.83 (20.61)	−3.33 (7.13)	1.92 [−4.82; 8.66]; 0.550
Total						Interaction	p value = 0.043
Vitality	24	63.89 (18.17)	11.11 (21.14)	26	53.21 (22.37)	−4.35 (19.60)	12.59 [3.76; 21.41]; 0.006 Hedges' g: 0.82 [0.23; 1.40]
Sex							
Men	11	65.91 (16.01)	8.33 (10.39)	10	51.67 (19.56)	3.70 (18.69)	1.70 [−13.61; 17.01]; 0.818
Women	13	62.18 (20.30)	13.64 (27.96)	16	54.17 (24.53)	−9.52 (19.02)	19.85 [7.48; 32.21]; 0.003 Hedges' g: 1.25 [0.43; 2.07]
Total						Interaction	p value = 0.036
Social limitations	24	73.15 (16.44)	5.82 (18.30)	26	66.24 (21.77)	0.48 (10.45)	6.61 [0.45; 12.76]; 0.036 Hedges' g:

Study VX11-770-110 Endpoint category Endpoint	IVA + BSC N[a]	IVA + BSC Values at start of study MV (SD)	IVA + BSC Change at the end of study[b] MV (SD)	Placebo + BSC N[a]	Placebo + BSC Values at start of study MV (SD)	Placebo + BSC Change at the end of study[b] MV (SD)	IVA + BSC vs. placebo + BSC MD [95% CI]; p value[i]
							0.61 [0.04; 1.18]
Sex							
Men	11	73.23 (16.07)	2.22 (14.63)	10	62.78 (22.69)	5.56 (9.21)	−2.43 [−12.39; 7.53]; 0.610
Women	13	73.08 (17.40)	9.09 (21.27)	16	68.40 (21.63)	−2.78 (10.16)	12.96 [3.66; 22.27]; p = 0.008 Hedges' g: 1.08 [0.28; 1.88]
Total						Interaction	p value = 0.022
Role function	24	90.97 (11.50)	3.57 (12.79)	26	78.85 (20.44)	−6.52 (19.62)	2.76 [−4.16; 9.68]; 0.425
Body image	24	89.81 (15.69)	3.17 (12.24)	26	86.32 (16.12)	−3.38 (13.16)	3.39 [−0.99; 7.77]; 0.126
Eating disorders	24	92.13 (15.18)	2.65 (15.68)	26	92.74 (11.31)	−6.76 (19.17)	5.04 [0.69; 9.39]; 0.024 Hedges' g: 0.66 [0.08; 1.23]
Therapy stress	24	75.00 (20.79)	1.06 (7.78)	26	61.11 (21.60)	5.80 (12.02)	−3.28 [−9.74; 3.18]; 0.312
Domain subjective health assessment	24	74.07 (16.60)	8.99 (18.80)	26	59.40 (25.52)	−1.45 (16.17)	6.22 [−2.47; 14.90]; 0.157

Study VX11-770-110 Endpoint category Endpoint	IVA + BSC N	IVA + BSC Patients with event n (%)	Placebo + BSC N	Placebo + BSC Patients with event n (%)	IVA + BSC vs placebo + BSC RR [95% CI]; p value
Side effects					
AE	24	23 (95.8)	26	26 (100)	–
SAE[k]	24	2 (8.3)	26	6 (23.1)	0.36 [0.08; 1.62]; 0.160
Discontinuation because of AE	24	0 (0)	26	0 (0)	–
Specific AE					
Oropharyngeal pain (PT, AE)	24	4 (16.7)	26	0 (0)	–; 0.033[l]

a: Number of patients included in the evaluation to calculate the effect; values at the start of study may be based on other patient numbers.
b: Refers to the change from the start of study at the last time of measurement
c: MMRM: Treatment, time of study, treatment×time of study as fixed effects; patient as random effect; adjusted for continuous values at the start of study of age and FEV_1 (as % of standardised normal value) as well as for the endpoint BMI according to BMI at the start of study; it remains unclear whether the result refers to the effect over all measurement points or to the difference at 24 weeks.
d: As % of the standardised normal value
e: Higher values indicate a better symptomatology; a positive group difference means an advantage for ivacaftor + BSC
f: 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)
g: Negative binomial model: Treatment as fixed effect, adjusted for continuous value at the start of study of FEV_1 (as % of standardised normal value) and log(study time) as "offset"
h: Calculation of the IQWiG
i: MMRM: treatment, time of study, treatment×time of study as fixed effects; patient as random effect; adjusted for continuous values at the start of study of age, FEV_1 (as % of standardised normal value), and respective CFQ-R domain score; 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.
g: Higher values indicate a better symptomatology/health-related quality of life; a positive group difference corresponds to an advantage for ivacaftor + BSC.
k: This includes events of the underlying disease (PT "Infectious pulmonary exacerbation of cystic fibrosis"); without recording these events, there is also no statistically significant difference between the treatment arms (1 patient with SAE cellulitis (PT) remains in the ivacaftor arm versus 0 patients with SAEs in the comparator arm)
l: Calculation by the IQWiG, unconditional exact test (CZS method); discrepancy between p value (exact) and CI (asymptotic) because of different calculation methods; no representation of effect estimation and CI because not informative.

Abbreviations:
BSC: best supportive care; 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; 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; 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.
Morbidity	↑	Advantage in respiratory system symptomatology.
Health-related quality of life	↑	Advantages in emotional state and vitality
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 from the age of 18 years with cystic fibrosis who have an R117H mutation in the CFTR gene

approx. 35–44 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 from the age of 18 years with cystic fibrosis who have an R117H mutation in the CFTR gene

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