Gemeinsamer Bundesausschuss

Ivacaftor (New Therapeutic Indication: Cystic Fibrosis, Patients ≥ 6 months to < 18 Years (R117H))

Resolution of: 17 December 2020 Valid until: unlimited
Entry into force on: 17 December 2020
Federal Gazette, BAnz AT 03 02 2021 B3

New therapeutic indication (according to the marketing authorisation of 9 June 2020):

Kalydeco granules are indicated for the treatment of infants aged at least 6 months, toddlers and children weighing 5 kg to less than 25 kg with cystic fibrosis (CF) who have an *R117H CFTR* mutation or one of the following gating (class III) mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R.*

Kalydeco tablets are indicated as monotherapy 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 an *R117H CFTR* mutation or one of the following gating (class III) mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R*.

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

Kalydeco is indicated for the treatment of patients from 6 months to < 18 years of age with cystic fibrosis (CF) who have an *R117H-CFTR* mutation.

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

a) Patients from 6 months to < 6 years of age with cystic fibrosis who have an *R117H* mutation in the *CFTR* gene:

Appropriate comparator therapy for ivacaftor as monotherapy:

- 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 ivacaftor compared with best supportive care:

Hint for a non-quantifiable additional benefit

b) Patients from 6 years to < 18 years of age with cystic fibrosis who have an *R117H* mutation in the CFTR gene:

Appropriate comparator therapy for ivacaftor as monotherapy:

- 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 ivacaftor compared with best supportive care:

Hint for a non-quantifiable additional benefit

Study results according to endpoints:[1]

a) Patients from 6 months to < 6 years of age with cystic fibrosis who have an *R117H* mutation in the *CFTR* gene:

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No differences relevant for the benefit assessment after transfer of evidence of the results of patients ≥ 18 years with the *R117H* mutation.
Morbidity	↑	Benefit after transfer of evidence of the results of patients ≥ 18 years with the *R117H* mutation.
Health-related quality of life	↑	Benefit after transfer of evidence of the results of patients ≥ 18 years with the *R117H* mutation.
Side effects	↔	No differences relevant for the benefit assessment considering the results of patients ≥ 6 months to < 6 years with gating mutations.
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 results

No suitable data were submitted for the benefit assessment.

[1] Data from the dossier assessment of the IQWiG (A20-52) unless otherwise indicated.

b) Patients from 6 years to < 18 years of age with cystic fibrosis who have an *R117H* mutation in the *CFTR* gene:

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	↑	Benefit after consideration of the results of patients ≥ 18 years with the *R117H* mutation.
Health-related quality of life	↑	Benefit after consideration of the results of patients ≥ 18 years with the *R117H* mutation.
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

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

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

Study 110 Endpoint category Endpoint	IVA + BSC		Placebo + BSC		IVA + BSC vs placebo + BSC
	N	Number of events n_E (n_E/patient years)	N	Number of events n_E (n_E/patient years)	Rate ratio [95% CI]; p value
Morbidity					
Pulmonary exacerbations (PE)	10	0 (0)a	9	0 (0)[a]	--
Hospitalisation because of PE	10	0 (0)[a]	9	0 (0)[a]	--

Study 110 Endpoint category Endpoint	IVA + BSC			Placebo + BSC			IVA + BSC vs. placebo + BSC
	N[b]	Values at start of study MV (SD)	Change at the end of study[c] MV (SD)	N[b]	Values at start of study MV (SD)	Change at the end of study[c] MV (SD)	MD [95% CI]; p value[d]
Morbidity							
FEV_1[e]							
Absolute change[f]	10	96.50 (8.69)	−3.02 (2.45)	9	93.39 (8.02)	4.71 (5.75)	−5.78 [−11.10; −0.45]; 0.035[g]
Relative change[f]	10	96.50 (8.69)	−2.97 (2.30)	9	93.39 (8.02)	5.24 (6.69)	−6.17 [−12.22; −0.12]; 0.046[g]
Body Mass Index (BMI)							
z-score[h] (absolute change)[i]	10	0.35 (0.99)	0.05 (0.43)	9	0.04 (0.89)	0.03 (0.39)	−0.07 [−0.26; 0.13]; 0.474[j]
Symptomatology (CFQ-R, domains on symptomatology)[k,l]							
Respiratory system	9	93.52 (6.94)	−1.39 (8.19)	8	89.93 (7.99)	3.57 (9.45)	−4.87 [−14.76; 5.01]; 0.303[m]
Gastrointestinal symptoms	8	77.78 (33.33)	16.67 (27.89)	8	87.50 (17.25)	4.76 (12.60)	0.49 [−6.88; 7.86]; 0.885[m]
Sweat chloride concentration (presented additionally)[n]							
[mmol/l] (absolute change)	9	61.94 (22.15)	−25.38 (15.09)	9	74.67 (26.77)	−2.69 (20.02)	−27.88 [−37.26; −18.49]; <0.0001[o]
Health-related quality of life							
CFQ-R (domains on health-related quality of life)[k,l]							
Physical well-being	9	88.89 (11.78)	−6.48 (32.09)	8	83.51 (12.78)	2.98 (13.14)	−11.73 [−29.63; 6.16]; 0.180 [m]
Emotional state	9	81.94 (6.91)	6.25 (9.77)	8	79.17 (16.06)	3.21 (9.83)	3.15 [−4.09; 10.40]; 0.365 [m]
Social limitations	9	64.29 (17.66)	10.32 (13.27)	8	64.48 (22.46)	4.08 (17.59)	7.13 [−3.24; 17.50]; 0.162 [m]
Body image	9	91.36 (10.80)	−3.70 (15.18)	8	90.28 (12.51)	6.35 (12.60)	−11.06 [−23.55; 1.43]; 0.078 [m]
Eating disorders	9	87.65 (23.20)	−5.56 (9.30)	8	75.00 (23.57)	12.70 (21.69)	13.74 [−4.46; 31.94]; 0.127 [m]
Therapy burden	9	71.61 (24.29)	11.11 (12.17)	8	58.33 (20.36)	14.29 (17.82)	−2.41 [−19.81; 15.00]; 0.768 [m]

Study 110 Endpoint category Endpoint	IVA + BSC		Placebo + BSC		IVA + BSC vs placebo + BSC
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Side effects[p]					
AEs (presented additionally)	10	8 (80.0)	9	9 (100.0)	–
SAEs	10	1 (10.0)[q]	9	0 (0)	2.73 [0.12; 59.57]; 0.523[r]
Discontinuation because of AEs	10	0 (0)	9	0 (0)	–

a. Derived on the basis of the number of patients with events; the pharmaceutical company describes in its dossier that it does not present analyses on the number of pulmonary exacerbations because no events occurred.
b. Number of patients included in the evaluation to calculate the effect; values at the start of study may be based on other patient numbers.
c. Refers to the change from the start of study at the last time of measurement
d. 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.
e. As % of the standardised normal value
f. Higher values indicate a better lung function; a positive group difference means an advantage for ivacaftor + BSC.
g. MMRM: Treatment, study time, and treatment×study time as fixed effects; patient as random effect; adjusted for continuous values of age and FEV1 (as % of standardised normal value) at the start of study
h. BMI adjusted for age and sex
i. Higher values mean a higher weight per square metre; a positive group difference means an advantage for ivacaftor + BSC.
j. MMRM: Treatment, study time, and treatment×study time as fixed effects; patient as random effect; adjusted for continuous values of age and FEV1 (as % of standardised normal value) and by BMI z-score at the start of study
k: Higher values indicate a better symptomatology/health-related quality of life; a positive group difference corresponds to an advantage for ivacaftor + BSC.
l. The domains weight problems (symptomatology) as well as role function, vitality, and subjective health assessment (health-related quality of life) are included exclusively in the questionnaires for patients ≥ 14 years; in the relevant sub-population (6 years to < 18 years), data were available for only 1 patient; the pharmaceutical company therefore did not present the results for these domains.
m. MMRM: Treatment, study time, and treatment×study time as fixed effects; patient as random effect; adjusted for continuous values of age, FEV1 (as % of standardised normal value), and respective CFQ-R domain score at the start of study
n. Data from the dossier of the pharmaceutical company.
o. MMRM: Treatment, round, and treatment × round as fixed effects, patient as random effect and adjustment according to continuous baseline values of chloride concentration in sweat, FEV1%, and age.
p. Survey of AEs in RCT VX11 770 110 in principle with events of the underlying disease; for the present dossier assessment, the pharmaceutical company submits evaluations without the event of the underlying disease "infectious pulmonary exacerbations of cystic fibrosis" (PT).
q. It cannot be excluded that the event that occurred in the ivacaftor + BSC arm (PT "constipation") was an event of the underlying disease.
r. own calculations of effect and CI (asymptotic) (in the case of 0 events in one study arm with correction factor 0.5 in both study arms); p value using unconditional exact test.

Abbreviations used:

BSC: best supportive care; BMI: body mass index; CFQ-R: Cystic Fibrosis Questionnaire – Revised; FEV1: 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_E: number of events, PT: preferred term; RCT: randomised controlled trial; RR: relative risk; SAE: serious adverse event; AE: adverse event; SD: standard deviation

2. Number of patients or demarcation of patient groups eligible for treatment

a) Patients from 6 months to < 6 years of age with cystic fibrosis who have an *R117H* mutation in the *CFTR* gene:

approx. 7 patients

b) Patients from 6 years to < 18 years of age with cystic fibrosis who have an *R117H* mutation in the *CFTR* gene:

approx. 19 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: 24 September 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:

a) Patients from 6 months to < 6 years of age 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	€ 196,555.50
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

b) Patients from 6 years to < 18 years of age 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	€ 196,555.50
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