Gemeinsamer Bundesausschuss

Ivacaftor (Exceeding the € 50 Million Limit: Cystic Fibrosis, Patients from 2 to 5 years)

Resolution of: 20 February 2020 Valid until: unlimited
Entry into force on: 20 February 2020
Federal Gazette, BAnz AT 07 04 2020 B2

Therapeutic indication (according to the product information of 19 April):

Ivacaftor is indicated for the treatment of children aged 12 months and older and a body weight between 7 and 25 kg 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.

This resolution concerns only the therapeutic indication for children aged 2 to 5 years with cystic fibrosis with one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R:

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

Children aged 2 to 5 years with cystic fibrosis who have one of the following gating (class III) mutations in the CFTR gene G551D, 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 the appropriate comparator therapy:

Hint for a non-quantifiable additional benefit.

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Study results according to endpoints:[1]

Children aged 2 to 5 years with cystic fibrosis who have one of the following gating (class III) mutations in the CFTR gene G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R:

Single-arm Study VX11-770-108 (ivacaftor + BSC) over 24 weeks and the expansion Study VX11-770-109 (ivacaftor + BSC) over another 84 weeks

Endpoint category Endpoint	Study VX11-770-108 Ivacaftor + BSC N	Patients with event after 24 weeks n (%)	Study VX11-770-109 Ivacaftor + BSC N	Patients with event after 84 weeks n (%)
Mortality				
Overall mortality				
	34	0 (0)	33[a]	0 (0)

Endpoint category Endpoint	Study VX11-770-108 Ivacaftor + BSC N	number of events (nE/patient years)	Study VX11-770-109 Ivacaftor + BSC N	number of events (nE/patient years)
Morbidity				
Pulmonary exacerbations				
Definition 1[b]	34	35 (2.27)	33[a]	40 (0.75[c])
Definition 2[b]	34	6 (0.39[c])	33[a]	9 (0.17[c])
Hospitalisations because of pulmonary exacerbations				
Definition 1[b]	34	4 (0.26[c])	33[a]	9 (0.17[c])
Definition 2[b]	34	0 (0)	33[a]	4 (0.07[c])

[1] Data from the dossier evaluation of the IQWiG (A19-67) unless otherwise indicated.

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Endpoint category Endpoint Study	Ivacaftor + BSC			
	Baseline		Mean change from baseline to week 24[d]	Mean change from baseline to week 84[e]
	N	MV (SD)	MV (SD)	MV (SD)
Morbidity				
Body Mass Index (BMI)				
BMI (age-dependent z-score, absolute change)				
VX11-770-108	32[f]	0.13 (0.80)	0.37 (0.42)	–[i]
VX11-770-109	28[f, g]	0.13 (0.81)	0.18 (0.60)	0.27 (0.64)
FEV_1 (absolute change) % [h]				
VX11-770-108	20	87.73 (16.83)	1.79 (17.81)	–[i]
VX11-770-109	24	87.8 (22.5)	–[j]	8.4 (18.3)
Sweat chloride concentration (absolute change) mmol/l[h] (additionally shown)				
VX11-770-108	30	97.88 (14.00)	−46.86 (26.19)	–[i]
VX11-770-109	31	51.6 (22.9)	–[j]	−8.5 (31.5)

Endpoint Category Endpoint Study	Ivacaftor + BSC
Health-related quality of life	
VX11-770-108	not collected
VX11-770-109	not collected

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Endpoint category Endpoint	Study VX11-770-108 Ivacaftor + BSC		Extension study VX11-770-109 Ivacaftor + BSC	
	N	Patients with event after 24 weeks n (%)	N	Patients with event after 84 weeks n (%)
Side effects				
AEs (additionally shown)[k]	34	33 (97.1)	33[a]	33 (100)
SAEs[k]	34	6 (17.6)	33[a]	11 (33.3)
Discontinuation because of AEs	34	1 (2.9)	33[a]	1 (3.0)

a: One patient with a dosage of 150 mg, which is not compliant with marketing authorisation

b: In the benefit assessment for ivacaftor, the definitions of pulmonary exacerbations are given in Table 17 on p. 50.

c: Calculation of the IQWiG.

d: In Study 109: a total of 48 weeks ivacaftor + BSC.

e: In Study 109: a total of 108 weeks ivacaftor + BSC.

f: Number of patients with values at both the start of study and last measurement time; the values at the start of study or earlier measurement time can be based on more patients.

g: Unclear whether one patient with a dosage of 150 mg, which is not compliant with marketing authorisation, is included

h: Data from the dossier of the pharmaceutical company.

i: No data collected.

j: The results were not shown in Module 4 of the dossier.

k: Contain events that are symptoms or consequences of the disease or for which it cannot be decided whether they are symptomatology/consequences of the disease or side effects.

BMI: Body Mass Index; BSC: best supportive care, FEV, forced expiratory volume n: patients with (at least 1) event; MV: mean value; N: number of patients evaluated; nE: number of events; SD: standard deviation; SAE: serious adverse event; AE: adverse event

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Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No differences relevant for the benefit assessment with evidence-based transfer of the results of patients ≥ 12 years with G551D gating mutation
Morbidity	↑	Advantage with evidence-based transfer of the results of patients ≥ 12 years with G551D gating mutation
Health-related quality of life	↑	Advantage with evidence-based transfer of the results of patients ≥ 12 years with G551D gating mutation
Side effects	↔	No differences relevant for the benefit assessment with evidence-based transfer of the results of patients ≥ 12 years with G551D gating 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

Children aged 2 to 5 years with cystic fibrosis who have one of the following gating (class III) mutations in the CFTR gene G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R:

Approx. 15 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

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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:

Children aged 2 to 5 years with cystic fibrosis who have one of the following gating (class III) mutations in the CFTR gene G551D, 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

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