Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V: Lumacaftor/ ivacaftor (reassessment after the deadline: cystic fibrosis, homozygous F508del mutation in CFTR gene, ≥ 2 to 5 years)

of 18 March 2022

At its session on 18 March 2022, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII is amended as follows:

1. The information on lumacaftor/ ivacaftor in the version of the resolution of 15 August 2019 (BAnz AT 09.09.2019 B2) is repealed.

2. Annex XII shall be amended in alphabetical order to include the active ingredient lumacaftor/ ivacaftor as follows:

Lumacaftor/ivacaftor

Resolution of: 18 March 2022
Entry into force on: 18 March 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 15 January 2019):

Orkambi granules are indicated for the treatment of cystic fibrosis (CF) in patients aged 2 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

Therapeutic indication of the resolution (resolution of 18 March 2022):

Orkambi granules are indicated for the treatment of cystic fibrosis (CF) in patients aged 2 to 5 years who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

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

Children with cystic fibrosis aged 2 to 5 years who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (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 (in particular antibiotics for pulmonary infections, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy (as defined in the Remedies Directive), making full use of all possible dietary measures).

Extent and probability of the additional benefit of lumacaftor/ ivacaftor compared to the best supportive care:

Hint for a non-quantifiable additional benefit

Study results according to endpoints:[1]

Children with cystic fibrosis aged 2 to 5 years who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant differences for the benefit assessment, even when considering the results in subjects ≥ 6 to < 12 years and ≥ 12 years.
Morbidity	↑	Advantage in BMI z-score, as well as advantages considering results in subjects ≥ 6 to < 12 years and ≥ 12 years.
Health-related quality of life	↔	No relevant differences for the benefit assessment considering the results in subjects ≥ 6 to < 12 years and ≥ 12 years.
Side effects	↔	No relevant differences for the benefit assessment, even when taking into account the results in subjects ≥ 6 to < 12 years and ≥12 years.

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

RCT VX16-809-121: Lumacaftor/ ivacaftor (LUM/IVA) vs BSC, 48 weeks

VX16-809-121 study	Lumacaftor/ ivacaftor + BSC		Placebo + BSC		Lumacaftor/ ivacaftor + BSC vs placebo + BSC
Endpoint category Endpoint	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Mortality					
Overall mortality	35	0 (0)	16	0 (0)	-

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A21-122) unless otherwise indicated.

VX16-809-121 study Endpoint category Endpoint	Lumacaftor/ ivacaftor + BSC			Placebo + BSC			Lumacaftor/ ivacaftor + BSC vs placebo + BSC
	N[a]	Values at the start of study MV (SD)	Change during week 48 MV (SE)	N[a]	Values at the start of study MV (SD)	Change during week 48 MV (SE)	MD [95% CI]; p value
Morbidity							
Lung Clearance Index ($LCI_{2,5}$)							
Absolute change	35	8.86 (2.01)	−0.38 (0.22)[b]	16	8.97 (2.42)	0.32 (0.32)[b]	-0.70 [-1.48; 0.07]; 0.075[c]
Body Mass Index (BMI)							
Absolute change [kg/m^2]	32	15.41 (1.28)	0.07 (0.65)[d]	16	15.77 (1.49)	-0.36 (0.61)[d]	0.43 [0.04; 0.82]; 0.033[e]
Age-dependent z-score, absolute change	32	-0.25 (1.14)	0.17 (0.10)[f]	16	0.06 (1.03)	-0.24 (0.15)[f]	0.41 [0.05; 0.77]; 0.027[g]
Sweat chloride concentration (presented additionally)[2]							
Absolute change (mmol/l)	34	104.01 (16.65)	77.77 (16.65)	16	100.59 (7.93)	101.88 (9.16)	-26.29 [-36.58; -15.99]; p < 0.001
MRI score (presented additionally)[2]							
MRI Global Chest Score[h]	34	17.65 (9.67)	16.0 (9.41)	15	21.40 (9.34)	21.13 (11.05)	-1.45 [-5.51; 2.61;] p=0.475
MRI Morphological Chest Score	34	13.65 (7.33)	12.75 (6.99)	15	17.00 (7.59)	16.07 (9.50)	-0.13 [-3.02; 2.76]; p = 0.929
MRI Perfusion Chest Score	34	4.00 (2.83)	3.25 (2.70)	16	4.31 (2.41)	4.81 (2.17)	-1.16 [-2.73; 0.42]; p = 0.147

[2] Data from the dossier

VX16-809-121 study Endpoint category Endpoint	Lumacaftor/ ivacaftor + BSC		Placebo + BSC		Lumacaftor/ ivacaftor + BSC vs placebo + BSC
	N	Number of events nE (nE/patient-years)[i]	N	Number of events nE (nE/patient-years)[i]	Rate Ratio [95% CI]; p value
Morbidity					
Pulmonary exacerbations	35	26 (0.75)	16	19 (1.17)	n.d.
Hospitalisation for pulmonary exacerbations	35	5 (0.14)	16	1 (0.06)	n.d.
	Lumacaftor/ ivacaftor + BSC		**Placebo + BSC**		**Lumacaftor/ ivacaftor + BSC vs placebo + BSC**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p value[j]**
Pulmonary exacerbations	35	15 (42.9)	16	10 (62.5)	0.69 [0.40; 1.18]; 0.170
Hospitalisation for pulmonary exacerbations	35	5 (14.3)	16	1 (6.3)	2.29 [0.29; 18.00]; 0.432

VX16-809-121 study Endpoint category Endpoint	Lumacaftor/ ivacaftor + BSC	Placebo + BSC	Lumacaftor/ ivacaftor + BSC vs placebo + BSC
Health-related quality of life			
VX16-809-121 study	not assessed		

VX16-809-121 study Endpoint category Endpoint	Lumacaftor/ ivacaftor + BSC N	Lumacaftor/ ivacaftor + BSC Patients with event n (%)	Placebo + BSC N	Placebo + BSC Patients with event n (%)	Lumacaftor/ ivacaftor + BSC vs placebo + BSC RR [95% CI]; p value
Side effects					
AEs[k] (presented additionally)	35	34 (97.1)	16	16 (100)	–
SAEs[k]	35	4 (11.4)	16	1 (6.3)	1.83 [0.22; 15.08]; 0.733[l]
Discontinuation due to AEs[k]	35	0 (0)	16	0 (0)	–

a) Number of patients who were taken into account in the evaluation for calculating the effect estimate; the values at start of study can be based on other patient numbers.
b) Mean change up to week 48: MV (SE) from MMRM
c) MMRM; effect represents the difference between the treatment groups of the changes averaged over the course of the study (up to week 48) between the respective time of measurement and the start of the study
d) Change at week 48: MV (SD) descriptive
e) IQWiG calculation from information on the change at week 48
f) Change at week 48: MV (SE) from MMRM
g) MMRM; effect represents the difference between the treatment groups of the change from the start of the study to week 48
h) Primary endpoint of the VX16-809-121 study
i) The pharmaceutical company calculates the event rate (nE/patient years) from the total number of events divided by the total number of years (sum of the duration of observation of all patients included in the analysis in days divided by 336).
j) Generalised linear model using the binomial distribution and a log-link function
k) Without PT "Infectious pulmonary exacerbation of cystic fibrosis"
l) p value: IQWiG calculation

Abbreviations:
BSC: Best supportive care; n.d.: no data available; CI: confidence interval; LCI: Lung Clearance Index; MD: mean difference; MMRM: mixed model for repeated measures; MV: mean value; n: number of patients with (at least 1) event; N: number of patients evaluated; nE: number of events; RCT: randomised controlled trial; RR: relative risk; SD: standard deviation; SE: standard error; SAE: serious adverse event; AE: adverse event

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

Children with cystic fibrosis aged 2 to 5 years who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

approx. 290 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 Orkambi (active ingredient: lumacaftor/ ivacaftor) at the following publicly accessible link (last access: 2 February 2022):

https://www.ema.europa.eu/en/documents/product-information/orkambi-epar-product-information_en.pdf

Treatment with lumacaftor/ ivacaftor should only be initiated and monitored by doctors experienced in the therapy of children with cystic fibrosis.

4. Treatment costs

Annual treatment costs:

Children with cystic fibrosis aged 2 to 5 years who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Lumacaftor/ivacaftor	€ 148,419.04
+ best supportive care	Different from patient to patient
Appropriate comparator therapy:	
Best supportive care	Different from patient to patient

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 1 March 2022)

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 18 March 2022.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 18 March 2022

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken