Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Ivacaftor (New Therapeutic Indication: Cystic Fibrosis, 6 to <12 Months)

of 4 June 2020

On 4 June 2020, the Federal Joint Committee (G-BA) resolved by written statement to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (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 on DD Month YYYY (Federal Gazette, BAnz AT DD MM YYYY BX), as follows:

I. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of ivacaftor in accordance with the resolution of 20 February 2020:

Ivacaftor

Resolution of: 4 June 2020
Entry into force on: 4 June 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 9 December 2019):

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

The present resolution relates exclusively to the newly approved therapeutic indication, i.e. children aged 6 to <12 months with cystic fibrosis with one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G5515, S1251N, S1255P, S549N, or S549R.

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

Children aged 6 to <12 months 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 best supportive care:

Hint for a non-quantifiable additional benefit

Study results according to endpoints:[1]

Children aged 6 to <12 months 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:

Study VX15-770-124: Single-arm study (ivacaftor + BSC) over 24 weeks

Endpoint category **Study VX15-770-124**	**Ivacaftor + BSC**
Mortality	
No deaths occurred.	

Endpoint category **Endpoint** **Study VX15-770-124**	**Ivacaftor + BSC**	
	N	**Number of events** **(n_E / patient years)**
Morbidity		
Pulmonary exacerbations Definition 1[a]	11	10 (1.95)
Pulmonary exacerbations Definition 2[a]	11	4 (0.78)

Endpoint category **Endpoint** **Study VX15-770-124**	**Ivacaftor + BSC**		
	Baseline		**Mean change from baseline to week 24[b]**
	N	**MV (SD)**	**MV (SD)**
Morbidity			
Ratio of body weight to body height			
Age-dependent z-score, absolute change	11	0.13 (0.85)	0.26 (1.30)
Percentile: absolute change	11	54.7 (27.8)	2.8 (38.3)

[1] Data from the dossier assessment of the IQWiG (**Fehler! Verwenden Sie die Registerkarte 'Start', um #Auftragsnummer_Q dem Text zuzuweisen, der hier angezeigt werden soll.**) unless otherwise indicated.

Endpoint category Endpoint Study VX15-770-124	Ivacaftor + BSC		
	Baseline		Mean change from baseline to week 24[b]
	N	MV (SD)	MV (SD)
Morbidity			
Sweat chloride concentration (additionally shown)			
Absolute change [mmol/l][c, d, e]	11[f]	101.5 (9.8)	-58.6 (16.5)

Endpoint category Study VX15-770-124	Ivacaftor + BSC
Health-related quality of life	
not collected	

Endpoint category Endpoint Study VX15-770-124	Ivacaftor + BSC	
	N	Number of patients with event after 24 weeks n (%)
Side effects		
AEs (additionally shown)[g]	11	10 (90.9)
SAEs[g]	11	3 (27.3))
Discontinuation due to AEs	11	0 (0)

a: In the benefit assessment for ivacaftor, the definitions of pulmonary exacerbations are given in Table 16 on p. 42.
b: Refers to the change from the start of study at the last time of measurement.
c: Data from the dossier of the pharmaceutical company.
d: Results with a sweat volume of < 15 µl or chloride concentrations in the sweat > 160 mmol/l are not included.
e: Five patients had baseline values of < 15 µl. These participants were not considered in the analysis. The MV were calculated over all participants who had measured values at the time of the survey.
f: Number of patients at the start of study.
g: 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.

Abbreviations used:
BSC: best supportive care; MV: mean value; MD: mean difference; n: number of patients with (at least one) event; N: number of patients evaluated; n_E: number of events; SD: standard deviation; (S)AE: (serious) 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 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 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

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

Children aged 6 to <12 months 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. 2 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:

Children aged 6 to <12 months 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: 15 May 2020

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 4 June 2020.

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

Berlin, 4 June 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken