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
Ivacaftor/ Tezacaftor/ Elexacaftor (new therapeutic indication: cystic fibrosis, combination regimen with ivacaftor, 6 to 11 years (homozygous for F508del mutation)

of 4 August 2022

At its session on 4 August 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. **In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of Ivacaftor/ Tezacaftor/ Elexacaftor in accordance with the resolution of 4 August 2022 (new therapeutic indication: cystic fibrosis, combination regimen with Ivacaftor, 6 to 11 years (heterozygous for F508del and MF mutations):**

Ivacaftor/ Tezacaftor/ Elexacaftor

Resolution of: 4 August 2022
Entry into force on: 4 August 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 7 January 2022):

Kaftrio is indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

Therapeutic indication of the resolution (resolution of 4 August 2022):

Kaftrio is indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis in patients aged 6 to 11 years who are homozygous for an F508del mutation in the CFTR gene.

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

Children aged 6 to 11 years with cystic fibrosis who are homozygous for the F508del mutation in the CFTR gene

Appropriate comparator therapy for Ivacaftor/ Tezacaftor/ Elexacaftor in combination with ivacaftor:

lumacaftor/ ivacaftor

or

tezacaftor/ ivacaftor in combination with ivacaftor

Extent and probability of the additional benefit of Ivacaftor/ Tezacaftor/ Elexacaftor in combination with Ivacaftor compared to the appropriate comparator therapy:

Hint for a non-quantifiable additional benefit

Study results according to endpoints:[1]

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 taking into account the results in patients aged 12 years and older
Morbidity	↑	Advantages in the endpoints of pulmonary exacerbations and the domains of respiratory system and weight problems of the CFQ-R, taking into account the results in patients 12 years and older
Health-related quality of life	↑	Advantages in the domains of physical well-being, vitality, role functioning, burden of therapy and subjective health assessment of the CFQ-R, taking into account the results in patients aged 12 years and older
Side effects	↔	No relevant differences for the benefit assessment, even when taking into account the results in patients aged 12 years and older
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		

VX18-445-106 study: single-arm marketing authorisation study of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor and BSC (children 6 to 11 years homozygous for the F508del mutation)

Mortality

Endpoint	IVA/ TEZ/ ELX + IVA + BSC	
	N	Patients with event n (%)
Overall mortality	29	0 (0)

Morbidity

Endpoint	IVA/ TEZ/ ELX + IVA + BSC

[1] Data from the dossier of the pharmaceutical company, unless otherwise indicated.

	N	Patients with event n (%)
Pulmonary exacerbation	29	0 (0)
Hospitalisation for pulmonary exacerbation	29	0 (0)

Endpoint	**IVA/ TEZ/ ELX + IVA + BSC**			
	N	Values at the start of the study MV (SD)	Values at week 24 MV (SD)	Mean change at week 24 MV (SD)
Lung Clearance Index ($LCI_{2,5}$)	25	10.26 (3.36)	9.27 (2.65)	-2.67 (2.32)
Forced expiratory one second volume (FEV_1%)	25	87.26 (18.31)	103.00 (10.76)	13.13 (10.76)
BMI ([kg/m^2], absolute change)	29	16.26 (1.61)	17.53 (1.80)	1.26 (0.85)
BMI (age-related z-score, absolute change)	29	-0.10 (0.61)	0.34 (0.52)	0.45 (0.35)
Sweat chloride concentration ([mmol/l], absolute change) *(presented additionally)*	26	99.25 (10.79)	33.95 (15.82)	-67.85 (13.79)
Domains of the symptomatology of the Cystic Fibrosis Questionnaire - Revised (CFQ-R) [children's version]				
Domain of respiratory system	28	81.85 (12.01)	92.22 (9.16)	10.00 (13.06)
Domain of gastrointestinal symptoms	28	75.00 (28.15)	93.33 (13.80)	15.56 (21.33)

Health-related quality of life

Endpoint	**IVA/ TEZ/ ELX + IVA + BSC**			
	N	Values at the start of the study MV (SD)	Values at week 24 MV (SD)	Mean change at week 24 MV (SD)
Domains on the health-related quality of life of the CFQ-R [children's version]				
Domain of physical well-being	28	85.32 (16.44)	90.00 (13.15)	-0.74 (8.62)
Domain of emotional state	28	76.34 (13.61)	86.39 (13.22)	5.28 (7.95)
Domain of body Image	28	88.10 (16.82)	97.78 (6.23)	2.96 (7.82)
Domain of eating disorders	28	90.08 (15.81)	92.59 (10.84)	3.70 (17.65)
Domain of burden of therapy	28	73.02 (22.92)	86.67 (14.67)	5.93 (16.19)
Domain of social limitations	28	67.18 (13.68)	57.56 (15.23)	-9.43 (18.97)

Side effects

Endpoint	IVA/ TEZ/ ELX + IVA + BSC	
	N	Patients with event n (%)
Adverse events (AEs)	29	29 (100)
Serious AEs (SAEs)	29	0 (0)
Severe AEs (grade 3 or 4)	29	1 (3.5)
Discontinuation due to AEs	29	0 (0)

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

Children aged 6 to 11 years with cystic fibrosis who are homozygous for the F508del mutation in the CFTR gene

approx. 470 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 Kaftrio (active ingredient: ivacaftor/ tezacaftor/ elexacaftor) at the following publicly accessible link (last access: 15 July 2022):

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

Treatment with 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 aged 6 to 11 years with cystic fibrosis who are homozygous for the F508del mutation in the CFTR gene

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Ivacaftor/ tezacaftor/ elexacaftor	€ 156,562.19
+ ivacaftor	€ 82,914.18 - € 82,970.63
Total:	€ 239,476.37 - € 239,532.81
Appropriate comparator therapy:	

Designation of the therapy	Annual treatment costs/ patient
Tezacaftor/ elexacaftor	€ 65,035.44
+ ivacaftor	€ 82,914.18 - € 82,970.63
Total:	€ 147,949.62 - € 148,006.07
or	
Lumacaftor/ ivacaftor	€ 148,419.04

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 July 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 4 August 2022.

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

Berlin, 4 August 2022

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

Prof. Hecken