Ivacaftor/ tezacaftor/ elexacaftor (new therapeutic indication: cystic fibrosis, combination regimen with ivacaftor, from 2 to ≤ 5 years (heterozygous for F508del and MF mutation))

Resolution of: 16 May 2024 valid until: unlimited
Entry into force on: 16 May 2024
Federal Gazette, BAnz AT 04 07 2024 B5

New therapeutic indication (according to the marketing authorisation of 22 November 2023):

Kaftrio granules are indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in paediatric patients aged 2 to less than 6 years who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

Therapeutic indication of the resolution (resolution of 16 May 2024):

Ivacaftor/ tezacaftor/ elexacaftor is indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis in paediatric patients aged 2 to ≤ 5 years who are heterozygous for an F508del mutation in the CFTR gene and carry a minimal function mutation on the second allele.

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

Children aged 2 to ≤ 5 years with cystic fibrosis who are heterozygous for the F508del mutation in the CFTR gene and carry a minimal function mutation on the second allele

Appropriate comparator therapy for ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor:

- 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 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]

Children aged 2 to ≤ 5 years with cystic fibrosis who are heterozygous for the F508del mutation in the CFTR gene and carry a minimal function mutation on the second allele

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant differences for the benefit assessment under transfer of evidence of the results from older patients and patients with heterozygous F508del and MF mutation
Morbidity	↑	Advantage under transfer of evidence of the results from older patients and patients with heterozygous F508del and MF mutation
Health-related quality of life	↑	Advantage under transfer of evidence of the results from older patients and patients with heterozygous F508del and MF mutation
Side effects	↔	No relevant differences for the benefit assessment under transfer of evidence of the results from older patients and patients with heterozygous F508del and MF 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 ∅: No data available. n.a.: not assessable		

VX20-445-111 study: single-arm approval study of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor (children 2 to 5 years; heterozygous for the F508del/MF mutation)

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

Mortality

Endpoint	IVA/ TEZ/ ELX + IVA	
	N	Patients with event n (%)
Overall mortality	52	0 (0)

Morbidity

Endpoint	IVA/ TEZ/ ELX + IVA	
	N	Patients with event n (%)
Pulmonary exacerbation	52	6 (11.54)
Hospitalisation for pulmonary exacerbation	52	0 (0)
With IV Pulmonary exacerbation requiring antibiotic treatment	52	0 (0)

Endpoint	IVA/ TEZ/ ELX + IVA				
	N	Values at the start of study MV (SD)	N	Values at week 24 MV (SD)	Mean change at week 24 MV (SD)
Absolute change in Lung Clearance Index ($LCI_{2,5}$)	34	8.53 (1.56)	32	7.55 (0.77)	-0.88 (1.44)
Absolute change in BMI [kg/m^2]	52	15.75 (0.98)	52	15.85 (1.09)	0.10 (0.58)
Absolute change in BMI z-score	52	0.05 (0.77)	52	0.19 (0.77)	0.14 (0.44)
Absolute change in sweat chloride concentration [mmol/l] *(presented additionally)*	49	100.80 (12.00)	43	48.93 (18.48)	-51.47 (20.19)

Health-related quality of life

Endpoint	IVA/ TEZ/ ELX + IVA
No data on health-related quality of life were collected.	

Side effects

Endpoint	IVA/ TEZ/ ELX + IVA	
	N	Patients with event n (%)
Adverse events (AEs) *(presented additionally)*	52	51 (98.08)
Serious AEs (SAEs)	52	1 (1.92)
Severe AEs (grade 3 or 4)	52	0 (0)
Discontinuation due to AEs	52	1 (1.92)

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

Children aged 2 to ≤ 5 years with cystic fibrosis who are heterozygous for the F508del mutation in the CFTR gene and carry a minimal function mutation on the second allele

approx. 160 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 April 2024):

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

Treatment with ivacaftor/ tezacaftor/ elexacaftor should only be initiated and monitored by doctors experienced in treating cystic fibrosis.

4. Treatment costs

Annual treatment costs:

Children aged 2 to ≤ 5 years with cystic fibrosis who are heterozygous for the F508del mutation in the CFTR gene and carry a minimal function mutation on the second allele

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Ivacaftor/ tezacaftor/ elexacaftor	€ 132,670.85
+ ivacaftor	€ 74,073.43
Total:	€ 206,744.28
+ 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: 15 April 2024)

Costs for additionally required SHI services: not applicable

5. Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

Children aged 2 to ≤ 5 years with cystic fibrosis who are heterozygous for the F508del mutation in the CFTR gene and carry a minimal function mutation on the second allele

- No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.