Gemeinsamer Bundesausschuss

Ivacaftor/tezacaftor/elexacaftor

Resolution of: 18 February 2021 valid until: unlimited
Entry into force on: 18 February 2021
Federal Gazette, BAnz AT 23.03.2021 B4

Therapeutic indication (according to the marketing authorisation of 21 August 2020):

Kaftrio is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene or heterozygous for F508del in the CFTR gene with a minimal function (MF) mutation.

Therapeutic indication of the resolution (resolution of 18 February 2021):

Kaftrio is used as a combination regimen with ivacaftor 150 mg tablets for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

1. Extent of the additional benefit and significance of the evidence

Patients aged 12 years and older with cystic fibrosis (CF) who are homozygous for the F508del mutation in the CFTR gene

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

Indication of a major 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 differences relevant for the benefit assessment.
Morbidity	↑↑	Advantages in the endpoints pulmonary exacerbations as well as the domains respiratory system and weight problems of the CFQ-R
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
Side effects	↔	No differences relevant for the benefit assessment.
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		

Study VX18-445-109 (parallel, double-blind RCT over 24 weeks): Ivacaftor/tezacaftor/elexacaftor + ivacaftor (IVA/TEZ/ELX + IVA) vs tezacaftor/ivacaftor + ivacaftor (TEZ/IVA + IVA)

Mortality

Study VX18-445-109 Endpoint category Endpoint	IVA/TEZ/ELX + IVA	TEZ/IVA + IVA	IVA/TEZ/ELX + IVA vs TEZ/IVA + IVA
Mortality			
No deaths occurred			

[1] Data from the dossier assessment of the G-BA (published on 1 December 2020) and from the amendment unless indicated otherwise.

Morbidity

Study VX18-445-109 Endpoint category Endpoint	IVA/TEZ/ELX + IVA		TEZ/IVA + IVA		IVA/TEZ/ELX + IVA vs TEZ/IVA + IVA
	N	Persons with event, n (%)	N	Persons with event, n (%)	RR[a] [95% CI]; p value
Morbidity					
Pulmonary exacerbations[b]					
Pulmonary exacerbations	87	10 (11.5)	88	36 (40.9)	0.28 [0.15; 0.53]; < 0.001
Serious pulmonary exacerbations[c]	87	1 (1.1)	88	9 (10.2)	0.11 [0.01; 0.87]; 0.010
Cystic Fibrosis Questionnaire-Revised (CFQ-R)[d]					
Respiratory system[e]	87	40 (46.0)	88	9 (10.2)	4.50[f] [2.32; 8.69]; < 0.0001
Gastrointestinal symptoms[e]	87	8 (9.2)	88	9 (10.23)	0.89[f] [0.36; 2.22]; 0.8179
Weight problems[g]	78	22 (28.21)	80	8 (10.0)	2.82[f] [1.34; 5.95]; 0.0065

Study VX18-445-109 Endpoint category Endpoint	IVA/TEZ/ELX + IVA				TEZ/IVA + IVA				IVA/TEZ/ELX + IVA vs TEZ/IVA + IVA
	Baseline[h]		Absolute Change at Week 24		Baseline[h]		Absolute Change at Week 24		MD[i] [95% CI]; p value; Hedges' g [95% CI]
	N	MV (SD)	N	MV (SD)	N	MV (SD)	N	MV (SD)	
Morbidity									
FEV1%									
FEV1 – absolute change	87	63.0 (16.7)	86	11.2 (0.7)	88	64.2 (15.1)	87	1.0 (0.7)	10.2 [8.2; 12.1]; < 0.0001
Sweat chloride concentration *(presented additionally)*									
Sweat chloride – absolute change	87	89.0 (12.2)	87	−46.2 (1.3)	88	89.8 (11.7)	88	−3.4 (1.2)	−42.8 [−46.2; −39.3]; < 0.0001

Study VX18-445-109 Endpoint category Endpoint	IVA/TEZ/ELX + IVA				TEZ/IVA + IVA				IVA/TEZ/ELX + IVA vs TEZ/IVA + IVA
	Baseline[h]		Absolute Change at Week 24		Baseline[h]		Absolute Change at Week 24		MD[i] [95% CI]; p value; Hedges' g [95% CI]
	N	MV (SD)	N	MV (SD)	N	MV (SD)	N	MV (SD)	
Body mass index (BMI)									
Absolute change in BMI	87	21.17 (3.43)	61	1.59 (0.13)	88	21.92 (3.89)	62	0.15 (0.13)	1.44 [1.07; 1.82]; < 0.0001
BMI (age dependent z-score)	28	−0.79 (0.98)	16	0.47 (0.11)	30	−0.33 (0.95)	19	−0.04 (0.10)	0.51 [0.20; 0.82]; 0.0018

Health-related quality of life

Study VX18-445-109 Endpoint category Endpoint	IVA/TEZ/ELX + IVA		TEZ/IVA + IVA		IVA/TEZ/ELX + IVA vs TEZ/IVA + IVA
	N	Persons with event, n (%)	N	Persons with event, n (%)	RR[j] [95% CI]; p value
Health-related quality of life					
Cystic Fibrosis Questionnaire-Revised (CFQ-R)[d]					
Physical well-being	87	24 (27.59)	88	7 (7.95)	3.47 [1.58; 7.63]; 0.002
Emotional state	87	8 (9.2)	88	6 (6.82)	1.35 [0.49; 3.72]; 0.564
Vitality[g]	78	25 (32.05)	80	13 (16.25)	1.97 [1.09; 3.57]; 0.0248
Social limitations	87	10 (11.49)	88	3 (3.41)	3.37 [0.96; 11.83]; 0.0578
Role functioning[g]	78	16 (20.51)	80	5 (6.25)	3.28 [1.26; 8.52]; 0.0147
Body image	87	11(12.64)	88	8 (9.09)	1.39 [0.59; 3.29]; 0.4528
Eating disorders	87	11 (12.64)	88	5 (5.68)	2.22 [0.81; 6.14]; 0.1224
Burden of therapy	87	19 (21.84)	88	8 (9.09)	2.40 [1.11; 5.19]; 0.0259

Subjective health assessment[g)]	78	26 (33.33)	80	8 (10.0)	3.33 [1.61; 6.91]; 0.0012

Side effects

Study VX18-445-109 Endpoint category Endpoint	IVA/TEZ/ELX + IVA		TEZ/IVA + IVA		IVA/TEZ/ELX + IVA vs TEZ/IVA + IVA
	N	Persons with event, n (%)	N	Persons with event, n (%)	RR[a)] [95% CI]; p value
Side effects[k)]					
AE (presented additionally)	87	77 (88.5)	88	75 (85.2)	-[l)]
AE CTCAE grade ≥ 3	87	6 (6.9)	88	4 (4.5)	1.52 [0.44; 5.19]; 0.507
SAE	87	4 (4.6)	88	6 (6.8)	0.67 [0.27; 2.31]; 0.53
Discontinuation because of AE	87	1 (1.1)	88	2 (2.3)	0.51 [0.05; 5.48]; 0.575
Skin and subcutaneous tissue disorders (SOC, AE)[c)]	87	20 (23.0)	88	4 (4.5)	5.06 [1.80; 14.19]; < 0.001[d]

a) Presentation in Module 4 without indication of the exact calculation of RR and p value.
b) Pulmonary exacerbations were recorded exclusively as PT in the context of the recording of AE.
c) Calculation taken from IQWIG benefit assessment (A20-77 and A21-03): Ivacaftor (new therapeutic indication: Cystic fibrosis, combination therapy with ivacaftor/tezacaftor/elexacaftor in patients 12 years and older (homozygous for F508del mutation))
d) Score: 0–100; higher values correspond a lower symptomatology/a better quality of life.
e) Pooled version "Children from 12 to 13 years" and "Adolescents and adults".
f) Generalised linear model with the variable "treatment group" using a binomial distribution with log-link function.
g) Not included in the questionnaire version for children.
h) Defined as the most recent non-missing measurement before the first dose of study medication in the treatment period.
i) LS mean difference based on an MMRM with treatment, round, treatment × round as fixed effects in the model and baseline FEV1% (< 70 vs ≥ 70%), age at screening (< 18 vs ≥ 18 years), and intake of CFTR modulators at screening (yes vs no) as covariates.
j) Generalised linear model with the variable "treatment group" using a binomial distribution with log-link function.
k) AE coded with the MedDRA Preferred Term "infective exacerbations of cystic fibrosis" were not included in the analysis because these events were explicitly reported as a separate endpoint.
l) Patient relevance cannot be clearly assessed.

Abbreviations: CFTR: Cystic Fibrosis Transmembrane Conductance Regulator; FEV1%: Proportion of forced one-second volume to standardised normal value in percent; IVA/TEZ/ELX: ivacaftor/tezacaftor/elexacaftor; CI: confidence interval; (S)AE: (serious) adverse event(s); MMRM: Mixed model for repeated measurements; MV: mean value; n: size of the sub-sample; N: total sample size; n.c.: not calculable; RR: relative risk; SD: standard deviation;

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

Patients aged 12 years and older with cystic fibrosis who are homozygous for the F508del mutation

approx. 2400 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: 9 February 2021):

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

Treatment with ivacaftor/tezacaftor/elexacaftor may be initiated and monitored only by specialists who are experienced in the treatment of patients with cystic fibrosis.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Ivacaftor/tezacaftor/elexacaftor	€ 158,139.51
+ ivacaftor	€ 100,977.84
Total costs	€ 259,117.35
Appropriate comparator therapy:	
Tezacaftor/ivacaftor	€ 78,708.73
+ ivacaftor	€ 100,977.84
Total costs:	€ 179,686.57
or	
Lumacaftor/ivacaftor	€ 148,415.91

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 February 2021

Costs for additionally required SHI services: not applicable