Gemeinsamer Bundesausschuss

Ivacaftor (New Therapeutic Indication: Cystic Fibrosis, Combination Therapy with Ivacaftor/Tezacaftor/Elexacaftor in Patients 12 Years and Older (Heterozygous for F508del and MF Mutation))

Resolution of: 18 February 2021 Valid until: unlimited
Entry into force on: 18 February 2021
Federal Gazette, BAnz AT 31 03 2021 B7

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

Kalydeco tablets are indicated in a combination regimen with ivacaftor /tezacaftor /elexacaftor tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis (CF) who are homozygous for the F508del mutation in the CFTR gene or heterozygous for F508del and have a minimal function (MF) mutation in the CFTR gene.

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

Kalydeco tablets are used in the framework of a combination regimen with ivacaftor/tezacaftor/elexacaftor tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis (CF) who are heterozygous for F508del and have a minimal function (MF) mutation in the CFTR gene.

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

Patients aged 12 years and older with cystic fibrosis who are heterozygous for a F508del mutation in the CFTR gene as well as a mutation with minimal function (MF) on the second allele

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

Best supportive care

Extent and probability of the additional benefit of ivacaftor in combination with ivacaftor/tezacaftor/elexacaftor compared with best supportive care:

Hint for a major additional benefit

Study results according to endpoints:[1]

Study VX17-445-102 (parallel, multi-centre, double-blind, randomised controlled over 24 weeks): Ivacaftor + ivacaftor/tezacaftor/elexacaftor (IVA/TEZ/ELX + IVA) + best supportive care (BSC) vs placebo + best supportive care (placebo +BSC)

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 endpoint pulmonary exacerbations and hospitalisation for pulmonary exacerbations as well as in the domains of the CFQ-R respiratory system and weight problems
Health-related quality of life	↑	Advantages in all domains of the CFQ-R in the quality of life category
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

Mortality

Study VX17-445-102 Endpoint category Endpoint	**IVA/TEZ/ELX + IVA + BSC**		**Placebo + BSC**		**IVA/TEZ/ELX + IVA + BSC vs Placebo + BSC**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p value**
Mortality					
No deaths occurred					

[1] Data from the dossier assessment of the IQWiG (A20-83) and from the addenda (A21-04 and G21-03) unless otherwise indicated.

Morbidity

Study VX17-445-102 Endpoint category Endpoint	IVA/TEZ/ELX + IVA + BSC		Placebo + BSC		IVA/TEZ/ELX + IVA + BSC vs Placebo + BSC
	N	Number of events nE (nE/patient years)[d]	N	Number of events nE (nE/patient years)[d]	Rate ratio [95% CI]; p value[e]
Morbidity					
Pulmonary exacerbations	200	41 (0.40[f])	203	113 (1.07[f])	0.37 [0.25; 0.55]; < 0.001
Hospitalisation because of pulmonary exacerbations	200	8[f] (0.08[f])	203	28[f] (0.26[f])	0.29 [0.14; 0.61]; no data available

Study VX17-445-102 Endpoint category Endpoint	IVA/TEZ/ELX + IVA + BSC			Placebo + BSC			IVA/TEZ/ELX + IVA + BSC vs Placebo + BSC
	N[g]	Values at start of study MV (SD)	Change at end of study[h] MV (SD)	N[g]	Values at start of study MV (SD)	Change at end of study[h] MV (SD)	MD [95% CI]; p value[i]
Morbidity							
Symptomatology – Cystic Fibrosis Questionnaire-Revised (CFQ-R)[j, k]							
FEV1%							
FEV_1[j] (absolute change)	200	61.65 (15.01)	13.98 (11.29)	203	61.25 (15.51)	−1.01 (7.17)	14.25 [12.73; 15.77]; < 0.001
Sweat chloride concentration [mmol/l] (presented additionally)[n]							
Sweat chloride (absolute change)	199	102.30 (11.85)	42.19 (0.92)	201	102.93 (9.78)	−0.35 (0.92)	−41.84 [−44.40; −39.28]; < 0.0001
Body Mass Index							
BMI ([kg/m²] absolute change)	200	21.49 (3.07)	1.12 (1.05)	203	21.31 (3.14)	0.09 (0.86)	1.04 [0.85; 1.23]; < 0.001

Study VX17-445-102 Endpoint category Endpoint	IVA/TEZ/ELX + IVA + BSC			Placebo + BSC			IVA/TEZ/ ELX + IVA + BSC vs Placebo + BSC
	N[g]	Values at start of study MV (SD)	Change at end of study[h] MV (SD)	N[g]	Values at start of study MV (SD)	Change at end of study[h] MV (SD)	MD [95% CI]; p value[i]
BMI (z-score, absolute change[m])	71	−0.37 (0.79)	0.36 (0.43)	74	−0.40 (0.98)	0.04 (0.37)	0.30 [0.17; 0.43]; < 0.001

Study VX17-445-102 Endpoint category Endpoint	IVA/TEZ/ELX + IVA + BSC			Placebo + BSC			IVA/TEZ/ ELX + IVA + BSC vs Placebo + BSC
	N	MV (SD)	Number of responders, n (%)	N	MV (SD)	Number of responders, n (%)	RR [95% CI]; p value
Morbidity							
Symptomatology – Cystic Fibrosis Questionnaire-Revised (CFQ-R)[j, k]							
Respiratory system	200	68.28 (16.91)	103 (51.5)	203	69.98 (17.76)	14 (6.9)	7.55 [4.48; 12.72]; < 0.001
Gastro-intestinal symptoms	200	83.06 (18.1)	29 (14.5)	203	83.36 (16.89)	25 (12.3)	1.17 [0.71; 1.92]; 0.535
Weight problems[k]	185	74.41 (30.99)	62 (33.5)	179	74.12 (31.71)	32 (17.9)	1.91 [1.31; 2.77]; < 0.001

Quality of life

Study VX17-445-102 Endpoint category Endpoint	IVA/TEZ/ELX + IVA + BSC			Placebo + BSC			IVA/TEZ/ ELX + IVA + BSC vs Placebo + BSC
	N	MV (SD)	Number of responders, n (%)	N	MV (SD)	Number of responders, n (%)	RR [95% CI]; p value

Health-related quality of life							
Symptomatology – Cystic Fibrosis Questionnaire-Revised (CFQ-R) [j, k, o]							
Physical well-being	200	76.5 (21.7)	51 (25.5)	203	76.4 (21.6)	12 (5.9)	4.38 [2.42; 7.94]; < 0.0001
Emotional state	200	82.05 (16.0)	22 (11.0)	203	80.2 (16.7)	8 (3.9)	2.77 [1.27; 6.07]; 0.011
Vitality[l]	185	62.8 (17.1)	46 (24.9)	179	63.8 (18.3)	6 (3.4)	7.51 [3.30; 17.07]; < 0.0001
Social limitations	200	70.5 (17.0)	34 (17.0)	203	68.8 (17.9)	10 (4.9)	3.48 [1.77; 6.83]; < 0.001
Role functioning[l]	185	81.7 (17.5)	30 (16.2)	179	83.3 (15.2)	7 (3.9)	4.17 [1.88; 9.23]; < 0.001
Body image	200	78.8 (22.1)	34 (17.0)	203	77.2 (23.5)	18 (8.9)	1.91 [1.12; 3.26]; 0.018
Eating disorders	200	90.0 (17.9)	22 (11.0)	203	89.1 (17.5)	11 (5.4)	2.06 [1.03; 4.10]; 0.04
Therapy stress	200	59.2 (19.2)	33 (16.5)	203	61.4 (20.2)	9 (4.4)	3.72 [1.83; 7.57]; < 0.001
Subjective health assessment[l]	185	63.5 (20.5)	77 (41.6)	179	64.2 (20.1)	10 (5.6)	7.49 [4.01; 14.00]; < 0.001

Side effects

Study VX17-445-102 Endpoint category Endpoint	**IVA/TEZ/ELX + IVA + BSC**		**Placebo + BSC**		**IVA/TEZ/ELX + IVA + BSC vs Placebo + BSC**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p value**
Side effects					
AEs[a]	202	187 (92.6)	201	187 (93.0)	–
AE Grade ≥ 3 or 4[n]	202	19 (9.4)	201	9 (4.5)	2.10 [0.97; 4.53]; 0.058
SAEs[a]	202	20 (9.9)	201	16 (8.0)	1.24 [0.66; 2.33]; 0.533[b]

Study VX17-445-102 Endpoint category Endpoint	IVA/TEZ/ELX + IVA + BSC		Placebo + BSC		IVA/TEZ/ELX + IVA + BSC vs Placebo + BSC
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Discontinuation because of AEs[a]	202	2 (1.0)	201	0 (0)	4.98 [0.24; 102.99];[c]; 0.212[b]

a. Without PT "Infectious pulmonary exacerbation of cystic fibrosis".
b. Own calculation: p value (unconditional exact test, CSZ method according to [16]
c. Own calculation: RR, CI (asymptotic) with correction factor of 0.5 in both study arms
d. The event rate (nE/patient-years) is calculated by dividing the total number of events by the total number of years (sum of the observation period of all patients included in the analysis).
e. Negative binomial model
f. Own calculation
g. Number of patients considered in the evaluation to calculate the effect estimate; the values in the course of the study and at the end of study may be based on other patient numbers.
h. Refers to the change from the start of study to the last time of measurement
i. MMRM: Treatment, study time, treatment × study time as fixed effects; adjusted for age, sex, and FEV1; effect represents the difference between the treatment groups of the changes averaged over the course of the study between the respective measurement time and start of study.
j. Higher values mean better symptomatology/health-related quality of life; a positive group difference means an advantage for ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC.
k. Domains on symptomatology, children [12 to 13 years] and adolescents or adults – pooled
l. Domain for adolescents or adults; not intended for children [12 to 13 years].
m. Only for patients ≤ 20 years of age
n. Calculation taken from G-BA benefit assessment ivacaftor/tezacaftor/elexacaftor in combination with ivacaftor, cystic fibrosis, in patients 12 years and older (heterozygous for F508del and MF mutation)
o. Improvement by at least 15 points. Evaluations for deterioration are not available.

Abbreviations used:
BSC: Best supportive care; CFQ-R: Cystic Fibrosis Questionnaire-Revised; ELEXA: elexacaftor; FEV1: forced expiratory volume in one second; IVA: ivacaftor; CI: confidence interval; MD: mean difference; MMRM: mixed model with repeated measurements; MV: mean value; n.c: not calculable; n.a.: not achieved; N: number of patients evaluated; n: Number of patients with (at least one) event; nE: number of events; PT: preferred term RCT: randomised controlled trial; RR: relative risk; SD: standard deviation; SAE: serious adverse event; TEZA: tezacaftor; AE: adverse event; vs: versus;

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

Patients aged 12 years and older with cystic fibrosis who are heterozygous for a F508del mutation in the CFTR gene as well as a mutation with minimal function (MF) on the second allele

approx. 1000 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: 1 February 2021):

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

Treatment with ivacaftor 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	€ 100,977.84
+ ivacaftor/tezacaftor/elexacaftor	€ 158,139.51
Total costs	€ 259,117.35
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: 1 February 2021

Costs for additionally required SHI services: not applicable