Ivacaftor (new therapeutic indication: cystic fibrosis, patients from 4 < 6 months, gating mutations)

Resolution of: 20 May 2021 Valid until: unlimited
Entry into force on: 20 May 2021
BAnz AT 21 06 2021 B5

New therapeutic indication (according to the marketing authorisation of 3 November 2020):

Kalydeco granules are indicated for the treatment of infants aged at least 4 months, toddlers and children weighing between 5 kg to less than 25 kg with cystic fibrosis (CF) who have an *R117H CFTR*-Mutation or one of the following gating (class III) mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N* or *S549R*.

Therapeutic indication of the resolution (resolution of 20 May 2021):

Kalydeco granules are indicated for the treatment of infants aged at least 4 < 6 months who have one of the following gating mutations (class III) in the *CFTR* gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R.

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

Infants with cystic fibrosis aged at least 4 to < 6 months 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 for ivacaftor:

- Best supportive care

Best Supportive Care (BSC) is defined as the therapy that ensures the best possible, patient-individually 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 compared to the appropriate comparator therapy:

Hint of non-quantifiable additional benefit

Study results according to endpoints:[1]

Infants with cystic fibrosis aged 4 to < 6 months who have any of the following gating mutations (class III) in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No differences relevant to benefit assessment under evidence transfer of outcomes from patients ≥ 12 years with G551D gating mutation.
Morbidity	↑	Benefits under evidence transfer of outcomes of patients ≥ 12 years with G551D gating mutation.
Health-related quality of life	↑	Benefits under evidence transfer of outcomes of patients ≥ 12 years with G551D gating mutation.
Side effects	↔	No differences relevant to benefit assessment under evidence transfer of outcomes from 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 is no usable data for the benefit assessment. n.a.: not assessable		

Study VX15-770-124 (Cohort 7): Single-arm study (ivacaftor + BSC) over 24 weeks

Endpoint category Endpoint	Ivacaftor + BSC
Mortality	
There were no deaths.	

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A20-100) unless otherwise indicated.

Endpoint category Endpoint	Ivacaftor + BSC	
	N	Number of events (n_E/patient years)
Morbidity		
Pulmonary exacerbations		
Definition[1a]	6	2 (0.73)
Definition 2a	6	1 (no data available)
Hospitalisations for pulmonary exacerbations		
Definition[1a]	6	1 (0.37)

Endpoint category Endpoint	Ivacaftor + BSC		
	Baseline		Mean change baseline to week 24[b]
	N	MV (SD)	MV (SD)
Morbidity			
Ratio of body weight to height			
age-dependent z-score, absolute change	6	-0.66 (0.97)	0.68 (1.12)
Sweat chloride concentration (presented additionally)			
Absolute change [mmol/l][d,e,f]	6	97.4 (16.4)	-50.0 (17.3)

Endpoint category	Ivacaftor + BSC
Health-related quality of life	
Not surveyed	

Endpoint category Endpoint	Ivacaftor + BSC	
	N	Number of patients with event after 24 weeks n (%)
Side effects		
AEs (presented additionally)[c]	6	6 (100)

SAEs[c]	6	1 (16.7)
Discontinuation because of	6	0 (0)

a: The definitions of pulmonary exacerbations are listed in the benefit assessment for ivacaftor A20-100 in Table 10 on page 29.
b: Refers to the change from the start of the study to the last time of measurement.
c: Events are included that are symptoms or consequences of the disease or for which it cannot be decided whether they are symptoms/consequences of the disease or side effects.
d: Information from the dossier of the pharmaceutical company.
e: Two patients had a missing baseline value. For these patients, historical measurements of chloride concentration in sweat were used as baseline values in the dossier.
f: For three patients no measurement is available at week 24: in one patient the sample was not collected; in two patients the amount of sweat collected was too low.

Abbreviations used:
BSC: Best supportive care; MV: Mean value; MD: Mean difference; n: number of patients with (at least 1) event; N: Number of patients evaluated; n_E: Number of events; SD: Standard deviation; (S)AE: (Serious) adverse events

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

Infants with cystic fibrosis aged at least 4 to < 6 months 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. 1 patient

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: 01 April 2021):
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:

Infants with cystic fibrosis aged at least 4 to < 6 months who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R

Name of therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Ivacaftor	€ 201,955.67
Best supportive care	Patient-individual
Appropriate comparator therapy:	
Best supportive care	Patient-individual

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

Costs for additionally required SHI services: not applicable