Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Nintedanib (New Therapeutic Indication: Other Chronic Fibrosing Interstitial Lung Diseases (ILDs) with a Progressive Phenotype)

of 4 February 2021

At its session on 4 February 2021 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), amended by the announcement on DD 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 nintedanib in accordance with the resolution of 17 October 2019:

Nintedanib

Resolution of: 4 February 2021
Entry into force on: 4 February 2021
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 13 July 2020):

Ofev is also indicated in adults for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype.

Therapeutic indication of the resolution (resolution of 4 February 2021):

Ofev is also indicated in adults for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype *[except idiopathic pulmonary fibrosis (IPF) and interstitial lung disease with systemic sclerosis (SSc-ILD)]*.

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

Adult patients with other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype

Appropriate comparator therapy:

- Best supportive care

Best supportive care is the therapy that ensures the best possible, patient-individual optimised, supportive treatment to alleviate symptoms and improve the quality of life.

Extent and probability of the additional benefit of nintedanib compared with best supportive care:

Indication of a minor additional benefit

Study results according to endpoints:[1]

Adult patients with other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype

[1] Data from the dossier assessment of the IQWiG (A20-71) and the addendum (A20-124) unless otherwise indicated.

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	↑	Advantage for acute exacerbations or death
Health-related quality of life	n.a.	The present data are not assessable.
Side effects	↓	Disadvantage in the endpoint therapy discontinuations because of AE as well as in detail in the specific AEs
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		

INBUILD study (RCT; nintedanib + BSC vs placebo + BSC)

INBUILD Study endpoint category Endpoint	Nintedanib + BSC		Placebo + BSC		Nintedanib + BSC vs Placebo + BSC
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p value
Mortality (overall study duration)[a)]					
Overall survival	332	n.a. 36 (10.8)	331	n.a. 45 (13.6)	0.78 [0.50; 1.21]; 0.259
Morbidity (overall study duration)[a)]					
acute exacerbation or death	332	n.a. 46	331	n.a. 65	0.67 [0.46; 0.98]; 0.039
acute exacerbation	332	no data available 23 (6.9)	331	no data available 35 (10.6)	0.63 [0.37; 1.07]; 0.087

INBUILD Study endpoint category Endpoint	Nintedanib + BSC			Placebo + BSC			Nintedanib + BSC vs placebo + BSC
	N[b)]	Values at start of study MV (SD)	Change at Week 52 MV (SE)	N[b)]	Values at start of study MV (SD)	Change at week 52 MV (SE)	MD [95% CI]; p value
Morbidity (52 weeks)							
Symptomatology (K-BILD	332	52.5 (11.0)	0.6 (0.6)	330	52.3 (9.9)	−0.8 (0.6)	1.34 [−0.31; 2.98]; 0.112
Health status (EQ-5D VAS[c)])	331	64.7 (20.0)	0.5 (1.0)	330	62.9 (19.6)	−2.2 (1.0)	2.62 [−0.03; 5.28]; 0.053

INBUILD study Endpoint category Endpoint	Nintedanib + BSC				Placebo + BSC				Nintedanib + BSC vs placebo + BSC
	N	Values at start of study MV (SD)	Week 52 MV (SD)	Annual decrease MV (SE)	N	Values at start of study MV (SD)	Week 52 MV (SD)	Annual Decrease MV (SE)	MD (SE) [95% CI]; p value
Morbidity									
Annual decrease of the forced vital capacity (FVC) [ml][2] (presented additionally)									
	332	2340.1 (740.2)	2271.8 (783.0)	−80.82 (15.07)	331	2321.1 (728.0)	2157.8 (733.0)	−187.78 (14.84)	106.96 (21.15) [65.42; 148.50]; < 0.001

INBUILD Study endpoint category Endpoint	Nintedanib + BSC	Placebo + BSC	Nintedanib + BSC vs placebo + BSC
Health-related quality of life (52 weeks)			
No usable data d)			

INBUILD study endpoint category Endpoint	Nintedanib + BSC		Placebo + BSC		Nintedanib + BSC vs placebo + BSC
	N	Patients with event n (%)	N	Patients and Patients with event n (%)	RR [95% CI]; p value
Side effects (overall study duration)[a)]					
AEs[e)] (presented additionally)	332	326 (98.2)	331	308 (93.1)	–
SAEs[e)]	332	140 (42.2)	331	151 (45.6)	0.92 [0.78; 1.10]; 0.530
Discontinuation because of AE	332	73 (22.0)	331	48 (14.5)	1.52 [1.09; 2.11]; 0.013
Gastrointestinal disorders[f)] (SOC, AEs)	332	279 (84.0)	331	164 (49.5)	1.70 [1.51; 1.91]; < 0.001

[2] Data from the dossier of the pharmaceutical company.

INBUILD study endpoint category Endpoint	Nintedanib + BSC N	Nintedanib + BSC Patients with event n (%)	Placebo + BSC N	Placebo + BSC Patients and Patients with event n (%)	Nintedanib + BSC vs placebo + BSC RR [95% CI]; p value
Diarrhoea (PT, severe AEs[g)])	332	33 (9.9)	331	6 (1.8)	5.48 [2.33; 12.91]; < 0.001
Hepatobiliary disorders[h)] (SOC, SAEs)	332	12 (3.6)	331	4 (1.2)	2.99 [0.97; 9.18]; 0.044
Reduced appetite (PT, AEs)	332	54 (16.3)	331	23 (6.9)	2.34 [1.47; 3.72]; < 0.001

a) Time at which the last randomised participant had completed the intended treatment duration of 52 weeks.
b) Number of patients with values at the start of the study. Presumably, this corresponds to the number of patients considered in the evaluation to calculate the effect estimate.
c) Higher (increasing) values mean lower symptomatology/better health status; positive effects ([nintedanib + BSC] – [placebo + BSC]) mean an advantage for nintedanib + BSC.
d) It was not possible to adequately assess the validity of the PF-IQOLS. The L-PF questionnaire is not considered sufficiently validated.
e) Without consideration of acute exacerbations
f) PTs that occurred within the SOC in ≥ 10% of patients in at least 1 study arm: Abdominal pain, diarrhoea, nausea and vomiting
g) Adapted from the operationalisation of the CTCAE grade ≥ 3
h) PTs that occurred within the SOC in ≥ 10 patients in at least 1 study arm: Abnormal liver function

BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; HR: hazard ratio; ILD: interstitial lung disease; K-BILD: King's Brief Interstitial Lung Disease Questionnaire; CI: confidence interval; L-PF: Living with Pulmonary Fibrosis; MD: mean difference; MV: mean value; n: number of patients with (at least 1) event; N: number of patients evaluated; n.a.: not achieved; PT: preferred term RCT: randomised controlled trial; RR: relative risk; SD: standard deviation; SE: standard error; SOC: system organ class; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale

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

Adult patients with other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype

approx. 4,500–11,400 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 Ofev (active ingredient: nintedanib) at the following publicly accessible link (last access: 16 December 2020):
https://www.ema.europa.eu/documents/product-information/ofev-epar-product-information_de.pdf

Treatment with nintedanib should be initiated and monitored only by specialists who are experienced in the treatment of patients with chronic fibrosing interstitial lung diseases with a progressive phenotype.

4. Treatment costs

Annual treatment costs:

Adult patients with other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Nintedanib	€ 39,690.47
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: 15 January 2021

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 4 February 2021.

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

Berlin, 4 February 2021

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken