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: Interstitial Lung Disease with Systemic Sclerosis (SSc-ILD))

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:

Courtesy translation – only the German version is legally binding.

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 17 April 2020):

Ofev is indicated in adults for the treatment of systemic sclerosis associated interstitial lung disease (SSc-ILD).

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

See new approved therapeutic indication

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

Adult patients with systemic sclerosis associated interstitial lung disease (SSc-ILD)

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:

An additional benefit is not proven.

Study results according to endpoints:[1]
Adult patients with systemic sclerosis associated interstitial lung disease (SSc-ILD)

[1] Data from the dossier assessment of the IQWiG (A20-70) unless otherwise indicated.

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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	↓	Disadvantage for intestinal problems (at least partly attributable to the side effects of nintedanib).
Health-related quality of life	↔	No differences relevant for the benefit assessment.
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		

SENSCIS study (RCT; nintedanib + BSC vs placebo + BSC)[2]

SENSCIS 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	149	n.a. 6 (4.0)	148	n.a. 7 (4.7)	0.93 [0.31; 2.77]; 0.895

[2] Sub-population "non-mycophenolate mofetil (MMF) population" considered for the benefit assessment: Patients who did not receive MMF therapy at the start of the study

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SENSCIS Study endpoint category Endpoint (Sub-)scale	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)							
FACIT-dyspnoea[c)]							
Shortness of breath score	147	45.6 (9.6)	0.89 (0.58)	146	44.5 (9.8)	0.61 (0.58)	0.28 [−1.34; 1.90]; 0.733
Functional limitations score	148	45.2 (9.2)	1.66 (0.56)	147	44.9 (9.8)	−0.06 (0.56)	1.73 [0.17; 3.28]; 0.030 Hedges' g: 0.27 [0.03; 0.51]
SHAQ[d)]							
HAQ-DI	146	0.51 (0.63)	0.08 (0.04)	145	0.56 (0.65)	0.03 (0.04)	0.05 [−0.05; 0.15]; 0.324
Pain VAS	135	2.60 (2.67)	0.11 (0.20)	141	2.59 (2.42)	−0.12 (0.20)	0.23 [−0.32; 0.79]; 0.406
Intestinal problems VAS	134	1.79 (2.59)	1.70 (0.22)	140	1.31 (2.03)	−0.25 (0.21)	1.95 [1.35; 2.55]; < 0.001 Hedges' g: 0.82 [0.57; 1.08]
Respiratory problems VAS	134	2.60 (2.65)	0.33 (0.19)	140	2.58 (2.71)	0.08 (0.19)	0.25 [−0.29; 0.79]; 0.357
Raynaud's syndrome VAS	133	2.69 (3.01)	0.43 (0.21)	140	2.99 (3.05)	−0.45 (0.21)	0.88 [0.29; 1.47]; 0.004 Hedges' g: 0.38 [0.12; 0.63]
Digital ulcerations VAS	133	1.28 (2.42)	0.58 (0.20)	140	1.52 (2.58)	−0.05 (0.20)	0.62 [0.06; 1.18]; 0.030 Hedges' g: 0.28 [0.03; 0.53]
Disease severity overall VAS	134	3.52 (2.74)	0.06 (0.20)	140	3.60 (2.74)	−0.22 (0.20)	0.27 [−0.29; 0.83]; 0.337
Health status (EQ-5D VAS)[e)]	149	68.51 (20.32)	−1.87 (1.45)	148	68.01 (18.89)	0.37 (1.45)	−2.24 [−6.28; 1.80]; 0.276
Health status (Patient Global Impression of Health VAS)[e)]	148	6.14 (2.05)	−0.30 (0.18)	147	6.28 (1.97)	0.09 (0.18)	−0.40 [−0.90; 0.10]; 0.120

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SENSCIS 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][3] (presented additionally)									
	149	2423.1 (747.8)	2386.3 (812.1)	−62.4 (20.0)	148	2503.4 (819.2)	2402.3 (803.3)	−118 (19.7)	55.58 (28.04) [0.38; 110.79]; 0.048

SENSCIS Study endpoint category Endpoint (Sub-)scale	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
Health-related quality of life (52 weeks)							
SGRQ total score[f)]	145	37.95 (19.71)	1.44 (1.21)	145	37.75 (21.89)	−0.35 (1.20)	1.79 [−1.57; 5.16]; 0.294

SENSCIS Study endpoint category Endpoint	Nintedanib + BSC		Placebo + BSC		Nintedanib + BSC vs Placebo + BSC
	N	Patients with event n (%)	N	Patients with event n (%)	OR [95% CI]; p value
Health-related quality of life (52 weeks)					
SGRQ responder[3] (presented additionally) Reduction by ≥ 4 points (WOCF analysis)	141	63 (44.7)	142	52 (36.3)	1.40 [0.87; 2.25]; 0.169

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

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SENSCIS Study endpoint category Endpoint	Nintedanib + BSC		Placebo + BSC		Nintedanib + BSC vs Placebo + BSC
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Side effects (overall study duration)[a), g)]					
AEs (presented additionally)	149	147 (98.7)	148	144 (97.3)	–
SAEs	149	43 (28.9)	148	51 (34.5)	0.84 [0.60; 1.17]; 0.306
Discontinuation because of AE	149	33 (22.1)	148	18 (12.2)	1.82 [1.07; 3.09]; 0.024
Gastrointestinal disorders[h)] (SOC, AEs)	149	133 (89.3)	148	85 (57.4)	1.55 [1.34; 1.80]; < 0.001
Diarrhoea (PT, severe AEs[i)])	149	18 (12.1)	148	4 (2.7)	4.47 [1.55; 12.89]; 0.002
Metabolism and nutrition disorders[j)] (SOC, AEs)	149	25 (16.8)	148	7 (4.7)	3.55 [1.58; 7.95]; < 0.001
Vascular disorders (SOC, AEs)	149	25 (16.8)	148	11 (7.4)	2.26 [1.15; 4.42]; 0.015

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a) Time at which the last randomised participant had completed the intended treatment duration of 52 weeks; however, maximum 100 weeks.
b) Number of patients who were taken into consideration in the evaluation for the calculation of the effect estimate; the values at the start of study (at other times, if necessary) can be based on other patient numbers.
c) Higher (increasing) values indicate a higher symptomatology; positive effects (intervention minus control) indicate a disadvantage for intervention. The Shortness of breath score can have a value between 27.7 and 75.9. The functional limitations score can have a value between 29.7 and 76.7.
d) Higher (increasing) values indicate a higher symptomatology; positive effects (intervention minus control) indicate a disadvantage for intervention. The HAQ-DI can have values from 0 to 3. The VAS scales can have values from 0 to 10.
e) Higher values mean better health status; positive effects (intervention – control) mean an advantage for intervention. The EQ-5D VAS can have values between 0 and 100, and the Patient Global Impression of Health VAS can have values between 0 and 10.
f) Higher (increasing) values mean worse quality of life; positive effects (intervention – control) mean a disadvantage for the intervention. The SGRQ total score can take values between 0 and 100 and includes 3 domains (symptoms, activity, and everyday stress).
g) Events that are attributable to the progression of the underlying disease are also recorded as AEs.
h) PTs that occurred within the SOC in ≥ 10 patients in at least 1 study arm: Abdominal pain, pain in upper abdomen, diarrhoea, nausea, and vomiting
i) Adapted from the operationalisation of the CTCAE grade ≥ 3
j) PTs that occurred within the SOC in ≥ 10 patients in at least 1 study arm: Reduced appetite

Abbreviations:
BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; FACIT-dyspnoea: Functional Assessment of Chronic Illness Therapy – dyspnoea; HAQ-DI: Health Assessment Questionnaire – Disability Index; CI: confidence interval; MD: mean difference; MMRM: mixed model with repeated measurements; MV: mean value; n: number of patients with (at least 1) event; N: number of patients evaluated; PT: preferred term RCT: randomised controlled trial; RR: relative risk; SD: standard deviation, SGRQ: St. George's Respiratory Questionnaire; SHAQ: Scleroderma Health Assessment Questionnaire; SOC: system organ class; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale; WOCF: worst observation carried forward

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

Adult patients with systemic sclerosis associated interstitial lung disease (SSc-ILD)

approx. 4,900 (200–10,700) 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):

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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 interstitial lung disease with systemic sclerosis (SSc-ILD).

4. Treatment costs

Annual treatment costs:

Adult patients with systemic sclerosis associated interstitial lung disease (SSc-ILD)

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

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