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 (reassessment of an orphan drug after exceeding the € 50 million limit)

of 17 October 2019

At its session on 17 October 2019, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (Pharmaceuticals Directive, AM-RL) in the version dated 18 December 2008/22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended on DD Month YYYY (Federal Gazette, BAnz AT DD MM YYYY BX), as follows:

I. Annex XII will be amended as follows:

1. The information relating to nintedanib as amended by the resolution of 3 September 2015 (Federal Gazette, BAnz AT 7 October 2015 B2) is hereby repealed.

2. Annex XII shall be amended in alphabetical order to include the active ingredient nintedanib as follows:

Nintedanib

Resolution of: 17 October 2019
Entry into force on: 17 October 2019
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 15 January 2015):

Ofev® is indicated in adults for the treatment of idiopathic pulmonary fibrosis

(IPF).

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

Adult patients with idiopathic pulmonary fibrosis

Appropriate comparator therapy:

Pirfenidone (only for patients with mild to moderate idiopathic pulmonary fibrosis according to marketing authorisation)

or 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:

Hint for a considerable additional benefit.

Study results according to endpoints:[1]

Adult patients with idiopathic pulmonary fibrosis

INPULSIS-1, INPULSIS-2, 1199.187, and TOMORROW studies (RCTs; nintedanib[2] + BSC vs placebo + BSC)

Endpoint category Endpoint Study	Nintedanib + BSC		Placebo + BSC		Nintedanib + BSC vs placebo + BSC
	N[a)]	Median time to event in weeks [95% CI]; Patients with event n (%)	N[a)]	Median time to event in weeks [95% CI]; Patients with event n (%)	HR [95% CI][b)]; p value[c)]
Mortality					
Overall survival					
INPULSIS-1	309	no data available; 13 (4.2)	204	no data available; 13 (6.4)	0.63 [0.29; 1.36]; 0.288
INPULSIS-2	329	no data available; 22 (6.7)	219	no data available; 20 (9.1)	0.74 [0.40; 1.35]; 0.300
1199.187	56	no data available; 1 (1.8)	57	no data available; 4 (7.0)	0.15 [0.02; 1.39]; 0.194
TOMORROW	86	no data available; 7 (8.1)	87	no data available; 9 (10.3)	0.73 [0.27; 1.98]; 0.538
Total					0.66 [0.37; 1.17]; 0.103
Morbidity					
Adjudicated acute exacerbations					
INPULSIS-1	309	no data available; 7 (2.3)	204	no data available; 8 (3.9)	0.55 [0.20; 1.54]; 0.302
INPULSIS-2	329	no data available; 5 (1.5)	219	no data available; 16 (7.3)	0.20 [0.07; 0.56]; 0.001
1199.187	56	no data available; 1 (1.8)	57	no data available; 2 (3.5)	0.39 [0.03; 4.91]; 0.576
TOMORROW[d)]	86	no data available; 2 (2.3)	87	no data available; 12 (13.8)	0.16 [0.04; 0.71]; 0.016
Total					0.29 [0.11; 0.77]; 0.028[e)]
Necessity of oxygen supply					
INPULSIS-1	Endpoint not recorded				
INPULSIS-2	Endpoint not recorded				
1199.187	Endpoint not recorded				
TOMORROW	86	no data available; 2 (2.3)	87	no data available; 3 (3.4)	0.66 [0.11; 4.00]; 0.652

[1] Data from the dossier evaluation of the IQWiG (A19-36) unless otherwise indicated.
[2] Dosage 2 × 150 mg/day

Endpoint category Endpoint Study	Nintedanib + BSC		Placebo + BSC		Nintedanib + BSC vs placebo + BSC
	N[a)]	Patients with event n (%)	N[a)]	Patients with event n (%)	RR [95% CI]; p value
Morbidity					
Change of respiratory state (PGI-C)[f)]					
INPULSIS-1	309	188 (60.84)	204	112 (54.90)	1.11 [0.95; 1.29][g)]
INPULSIS-2	329	203 (61.70)	219	118 (53.88)	1.15 [0.99; 1.33][g)]
1199.187	Endpoint not recorded				
TOMORROW	Endpoint not recorded				
Total					1.13 [1.01; 1.25]; 0.028 [h)]

Endpoint category Endpoint Study	Nintedanib + BSC				Placebo + BSC				Nintedanib + BSC vs placebo + BSC
	N	Values at start of study MV (SD)	weeks 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] (additionally shown:)									
INPULSIS 1	309	2756.8 (735.12)	2669 (772.04)	114.65 (15.33)	204	2844.5 (820.11)	2669.0 (772.04)	239.91 (18.71)	125.26 (24.21) [77.68; 172.84]; < 0.0001
INPULSIS 2	329	2672.8 (775.96)	2637.3 (811.80)	113.59 (15.73)	219	2619.0 (787.35)	2512.5 (821.44)	207.32 (19.31)	93.73 (24.91) [44.78; 142.68]; 0.0002
1199.187	56	2996.81 (831.25)	no data available	−9.35 (58.50)	57	2921.26 (833.91)	no data available	185.72 (57.36)	195.07 (82.26) [31.87; 358.26] 0.0196
Total									112.42 (16.998) [79.06; 145.77]; < 0.0001

[3] Data from the dossier of the pharmaceutical company. The TOMORROW study is not included by the pharmaceutical company in the dossier for the derivation of the additional benefit. Consequently, no data are available for the decrease in FVC in the TOMORROW study.

Endpoint category Endpoint Study	Nintedanib + BSC			Placebo + BSC			Nintedanib + BSC vs placebo + BSC
	N[i)]	Values at start of study MV (SD)	Change at the end of study MV (SE)	N[i)]	Values at start of study MV (SD)	Change at the end of study MV (SE)	MD [95% CI]; p value *Hedges' g [95% CI]*
Morbidity							
Endurance (6 minutes walk test), [m])[j)]							
INPULSIS-1				Endpoint not recorded			
INPULSIS-2				Endpoint not recorded			
1199.187	55	345.46 (140.71)	4.93 (11.43)[k)]	52	347.69 (146.26)	−13.01 (11.49)[k)]	17.93 [−14.26; 50.12]; 0.272[k)]
TOMORROW	63	437.0 (13.69)[l)]	−29.35 (12.96)[m)]	69	411.1 (15.90)[l)]	−35.67 (12.73)[m)]	6.32 [−27.08; 39.72]; 0.710[m)]
Total							–[n)]
Coughing (CASA-Q)[o)]							
Coughing symptoms							
INPULSIS-1	302[p)]	58.63 (23.59)	−0.76 (1.14)[k)]	202[p)]	56.29 (22.86)	−0,52 (1.40)[k)]	−0.24 [−3.78; 3.30]; 0.894[k)]
INPULSIS-2	323[p)]	61.60 (23.89)	−0.33 (1.09)[k)]	215[p)]	62.52 (21.42)	−2,38 (1.33)[k)]	2.05 [−1.31; 5.41]; 0.233[k)]
1199.187				Endpoint not recorded			
TOMORROW				Endpoint not recorded			
Total							0.95 [−1.49; 3.38]; 0.445[q)]
Coughing burden							
INPULSIS-1	302[p)]	74.22 (22.84)	−2.36 (1.01)[k)]	202[p)]	74.18 (22.34)	−4,00 (1.24)[k)]	1.64 [−1.49; 4.77]; 0.304[k)]
INPULSIS-2	322[p)]	75.55 (24.12)	−2.58 (0.99)[k)]	215[p)]	77.04 (21.88)	−4,39 (1.21)[k)]	1.81 [−1.26; 4.88]; 0.248[k)]
1199.187				Endpoint not recorded			
TOMORROW				Endpoint not recorded			
Total							1.73 [−0.46; 3.92]; 0.121[q)]
Dyspnoea (SOBQ)[r)]							
INPULSIS-1	267	32.58 (22.98)	6,73 (1.11)[k)]	178	32.24 (23.35)	7,61 (1.38)[k)]	−0.88 [−4.35; 2.60]; 0.620[k)]
INPULSIS-2	302	33.10 (25.70)	6,69 (1.07)[k)]	204	33.53 (24.08)	9,07 (1.30)[k)]	−2.38 [−5.68; 0.93]; 0.159[k)]
1199.187	53	25.39 (19.89)	3,42 (2.07)[k)]	50	42.25 (24.55)	−2,48 (2.10)[k)]	5.90 [−0.15; 11.95]; 0.056[k)]
TOMORROW				Endpoint not recorded			
Total							–[n)]
Health status (EQ-5D VAS)[s)]							
INPULSIS-1	293[p)]	66.71 (17.42)	−2.95 (0.94)[k)]	197[p)]	68.02 (16.34)	−6.04 (1.17)[k)]	3.09 [0.14; 6.03]; 0.040[k)]
INPULSIS-2	312[p)]	69.77 (18.85)	−2.50 (0.91)[k)]	211[p)]	67.75 (16.47)	−6,90 (1.11)[k)]	4.39 [1.59; 7.20]; 0.002[k)]
1199.187				Endpoint not recorded			

Endpoint category Endpoint Study	Nintedanib + BSC N[i)]	Values at start of study MV (SD)	Change at the end of study MV (SE)	Placebo + BSC N[i)]	Values at start of study MV (SD)	Change at the end of study MV (SE)	Nintedanib + BSC vs placebo + BSC MD [95% CI]; p value *Hedges' g [95% CI]*
TOMORROW	Endpoint not recorded						
Total							3.81 [1.78; 5.85]; < 0.001[q)] *0.25 [0.12; 0.39][t)]*

Endpoint category Endpoint Study	Nintedanib + BSC N[a]	Values at start of study MV (SD)	Change at end of study MV (SE)	Placebo + BSC N[a]	Values at start of study MV (SD)	Change at end of study MV (SE)	Nintedanib + BSC vs placebo + BSC MD [95% CI]; p value *Hedges' g [95% CI]*
Health-related quality of life							
SGRQ total score[u)] (additionally shown)							
INPULSIS-1	289	39.55 (17.63)	4,34 (0.80)[k)]	200	39.79 (18.48)	4,39 (0.96)[k)]	−0.05 [−2.50; 2.40]; 0.966[k)]
INPULSIS-2	320	39.46 (20.47)	2,80 (0.73)[k)]	213	39.39 (18.65)	5,48 (0.89)[k)]	−2.69 [−4.95; −0.43]; 0.020[k)] *−0.21 [−0.38; −0.03][t)]*
1199.187	55	35.75 (17.49)	−2,44 (1.54)[k)]	53	44.39 (18.49)	−2,75 (1.55)[k)]	0.31 [−4.10; 4.72]; 0.889[k)]
TOMORROW	75	40.2 (2.09)[l)]	−0.66 (1.71)[m)]	79	41.8 (2.03)[l)]	5.46 (1.73)[m)]	−6.12 [−10.57; −1.67]; 0.007[m)] *−0.43 [−0.75; −0.11][t)]*
Total							–[n)]

Endpoint category Endpoint Study	Nintedanib + BSC N[a]	Patients with event n (%)	Placebo + BSC N[a]	Patients with event n (%)	Nintedanib + BSC vs placebo + BSC RR [95% CI]; p value
Health-related quality of life					
SGRQ responder (reduction by ≥ 4 points)[4]					
INPULSIS-1 (52 weeks)	309	63 (20.39)	204	49 (24.02)	0.85 [0.61; 1.18]; 0.351
INPULSIS-2 (52 weeks)	329	83 (25.23)	219	37 (16.89)	1.49 [1.05; 2.11]; 0.022
1,199,187 (24 weeks)	56	14 (25.00)	57	22 (38.60)	0.65 [0.37; 1.13]; 0.132
TOMORROW (52 weeks)	86	25 (29.1)	87	14 (16.1)	1.81 [1.01; 3.23]; 0.048
Total					*Heterogeneity: Q = 11.62; p value = 0.009; I² =*

[4] Data from the addendum of the IQWiG (A19-64) unless otherwise indicated.

Endpoint category Endpoint Study	Nintedanib + BSC		Placebo + BSC		Nintedanib + BSC vs placebo + BSC
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p value
					74.20%

Endpoint category Endpoint Study	Nintedanib + BSC		Placebo + BSC		Nintedanib + BSC vs placebo + BSC
	N[v)]	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[w)]
Side effects					
AEs (additionally shown)					
INPULSIS-1	309	298 (96.4)	204	181 (88.7)	–
INPULSIS-2	329	311 (94.5)	219	198 (90.4)	–
1199.187	56	55 (98.2)	57	52 (91.2)	–
TOMORROW	85	80 (94.1)	85	77 (90.6)	–
SAEs					
INPULSIS-1	309	96 (31.1)	204	55 (27.0)	1.15 [0.87; 1.53]; 0.318
INPULSIS-2	329	98 (29.8)	219	72 (32.9)	0.91 [0.70; 1.17]; 0.444
1199.187	56	8 (14.3)	57	9 (15.8)	0.90 [0.38; 2.18]; 0.823
TOMORROW	85	23 (27.1)	85	26 (30.6)	0.88 [0.55; 1.42]; 0.682[x)]
Total					0.99 [0.79; 1.23]; 0.866[e)]
Discontinuation because of AEs					
INPULSIS-1	309	65 (21.0)	204	22 (10.8)	1.95 [1.24; 3.06]; 0.002
INPULSIS-2	329	58 (17.6)	219	33 (15.1)	1.17 [0.79; 1.73]; 0.430
1199.187	56	8 (14.3)	57	3 (5.3)	2.71 [0.76; 9.71]; 0.106
TOMORROW	85	26 (30.6)	85	22 (25.9)	1.18 [0.73; 1.91]; 0.532[x)]
Total					1.44 [0.86; 2.40]; 0.109[e)]

Endpoint category Endpoint Study	Nintedanib + BSC		Placebo + BSC		Nintedanib + BSC vs placebo + BSC
	N[v)]	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[w)]
Gastrointestinal disorders (SOC)					
INPULSIS-1	309	235 (76.1)	204	71 (34.8)	2.19 [1.79; 2.66]; < 0.001[x)]
INPULSIS-2	329	253 (76.9)	219	97 (44.3)	1.74 [1.48; 2.04]; < 0.001[x)]
1199.187	56	48 (85.7)	57	30 (52.6)	1.63 [1.25, 2.13]; < 0.001[x)]
TOMORROW	85	63 (74.1)	85	27 (31.8)	2.33 [1.67; 3.26]; < 0.001[x)]
Total					1.92 [1.48; 2.49]; 0.004[e)]
Contained therein:					
Diarrhoea (PT)					
INPULSIS-1	309	190 (61.5)	204	38 (18.6)	3.30 [2.45; 4.46]; < 0.001
INPULSIS-2	329	208 (63.2)	219	40 (18.3)	3.46 [2.58; 4.64]; < 0.001
1199.187	56	40 (71.4)	57	21 (36.8)	1.94 [1.33; 2.83]; < 0.001
TOMORROW	85	47 (55.3)	85	13 (15.3)	3.62 [2.12; 6.18]; < 0.001[x)]
Total					2.99 [1.90; 4.70]; 0.005[e)]
Nausea (PT)					
INPULSIS-1	309	70 (22.7)	204	12 (5.9)	3.85 [2.14; 6.92]; < 0.001
INPULSIS-2	329	86 (26.1)	219	16 (7.3)	3.58 [2.16; 5.93]; < 0.001
Study 1199.187	56	16 (28.6)	57	13 (22.8)	1.25 [0.67; 2.36]; 0.483
TOMORROW	85	20 (23.5)	85	8 (9.4)	2.50 [1.17; 5.36]; 0.014[x)]
Total					Heterogeneity[y)]: Q = 8.57; p value = 0.036; I^2: 65.0 %
Vomiting (PT)					
INPULSIS-1	309	40 (12.9)	204	4 (2.0)	6.60 [2.40; 18.2]; < 0.001
INPULSIS-2	329	34 (10.3)	219	7 (3.2)	3.23 [1.46; 7.16]; 0.002
Study 1199.187	56	9 (16.1)	57	3 (5.3)	3.05 [0.87; 10.70]; 0.062
TOMORROW	85	11 (12.9)	85	4 (4.7)	2.75 [0.91; 8.30]; 0.065[x)]
Total					3.69 [1.99; 6.83]; 0.007[e)]
Upper abdominal pain (PT)					
INPULSIS-1	309	23 (7.4)	204	9 (4.4)	1.69 [0.80; 3.57]; 0.187[x)]
INPULSIS-2	329	18 (5.5)	219	6 (2.7)	2.00 [0.81; 4.95]; 0.135[x)]
Study 1199.187	56	3 (5.4)	57	3 (5.3)	1.02 [0.21; 4.83][x)]; no data available
TOMORROW	85	10 (11.8)	85	3 (3.5)	3.33 [0.95; 11.69]; 0.046[x)]
Total					1.88 [1.06; 3.32]; 0.039[e)]

a) All randomised patients (INPULSIS 1 and INPULSIS 2 studies) or those for whom the intake of at least one dose of the study medication has been documented (1199.187 and TOMORROW studies)
b) Effect and CI calculated using Cox proportional hazards model, adjusted for treatment, sex, age, and height; in the TOMORROW study, additionally adjusted by region
c) p value calculated using log rank test.
d) In the TOMORROW study, no subsequent adjudication of exacerbations was performed; non-adjudicated acute exacerbations were therefore used for this study.
e) Calculation of the IQWiG from meta-analysis with random effects (Knapp-Hartung method)
f) Responders defined as “much much better”, “much better”, “a little better”, or “no change”. Missing values were classified as non-responders.
g) Calculation of the IQWiG of relative risk, CI (asymptotic)
h) Calculation of the IQWiG, from meta-analysis with fixed effect.
i) Number of patients who were taken into account in the evaluation for the calculation of the estimation of the effect; the values at the start of study (at other times, if necessary) can be based on other patient figures.
j) A negative change means a worse endurance; a positive group difference corresponds to an advantage for nintedanib + BSC.
k) MMRM evaluation adjusted for treatment, round, value at baseline and study participants, and interaction terms for treatment and round, value at baseline and visit.
l) Standard error
m) ANCOVA with replacement of missing values according to LOCF; adjusted for treatment, value at baseline, and region.
n) Analysis by a suitable model with meaningful interpretable effect estimation and confidence interval not available
o) A higher value means fewer cough symptoms or less stress from coughing; a negative group difference corresponds to a disadvantage for nintedanib + BSC.
p) Module 4 A contains a higher number of patients included in the evaluation than Module 5 of the dossier. The information from Module 5 is shown here.
q) Meta-analysis of the pharmaceutical company based on individual patient data
r) A low total value means a lower impairment because of shortness of breath; a negative group difference corresponds to an advantage for nintedanib + BSC.
s) A higher value means a better health status; a positive group difference corresponds to an advantage for nintedanib + BSC.
t) IQWiG calculation based on effect estimation of mean difference and CI of the MMRM or ANCOVA or meta-analysis with fixed effect
u) A higher value means a higher impairment; a negative group difference corresponds to an advantage for nintedanib + BSC.
v) Patients for whom the intake of at least one dose of the study medication has been documented (treated set)
w) χ^2 test
x) Calculation of the IQWiG: RR, CI (asymptotic) and p value (unconditional exact test, CSZ method).
y) Q test for heterogeneity

Abbreviations used:

BSC: best supportive care; CASA-Q: Cough and Sputum Assessment Questionnaire; EQ-5D: European Quality of Life – 5 Dimensions; CI: confidence interval; LOCF: last observation carried forward; MMRM: mixed model with repeated measurements; MD: mean difference; MV: mean value; m: metres; N: number of patients evaluated; n: number of patients with (at least 1) event; PGI-C: Patient’s Global Impression of Change; PT: preferred term; RCT: randomised controlled trial; RR: relative risk; SD: standard deviation; SE: standard error; SGRQ: St. George’s Respiratory Questionnaire; SOBQ Shortness of Breath Questionnaire; SOC: system organ class; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale; vs: versus

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

Adult patients with idiopathic pulmonary fibrosis

Approx. 1,800–18,900 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: 31 July 2019): https://www.ema.europa.eu/documents/product-information/ofev-epar-product-information_de.pdf

Treatment with nintedanib should only be initiated and monitored by specialists who are experienced in the treatment of patients with idiopathic pulmonary fibrosis (IPF).

4. Treatment costs

Annual treatment costs:

Adult patients with idiopathic pulmonary fibrosis

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Nintedaniv (Ofev®)	€ 36,321.15
Appropriate comparator therapy:	
Pirfenidone[5]	€ 37,387.78
Best supportive care	different for each individual patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 September 2019

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 17 October 2019.

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

[5] only for patients with mild to moderate idiopathic pulmonary fibrosis according to marketing authorisation

Berlin, 17 October 2019

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The chair

Prof Hecken