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Nintedanib (other chronic progressive fibrosing interstitial lung diseases) –

Addendum to Commission A20-71[1]

Addendum

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Table of contents

List of tables

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ATAQ-IPF	A Tool to Assess Quality of Life in IPF
BSC	best supportive care
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IPF	idiopathic pulmonary fibrosis
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
L-PF	Living with Pulmonary Fibrosis
PF-ILD	progressive fibrosing interstitial lung disease

1 Background

On 22 December 2020, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A20-71 (Nintedanib – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier, the pharmaceutical company (hereinafter referred to as the "company") presented study 1199.247 (hereinafter referred to as "INBUILD") for the assessment of the added benefit of nintedanib in comparison with the appropriate comparator therapy (ACT) best supportive care (BSC) in adults with other chronic progressive fibrosing interstitial lung diseases (PF-ILD) [2]. This study used the Living with Pulmonary Fibrosis (L-PF) questionnaire to record morbidity and health-related quality of life. However, Module 4 A did not provide sufficient information to assess the validity of the L-PF for patients with PF-ILD. Since the L-PF was developed for the therapeutic indication of PF-ILD and appeared to be suitable for representing symptoms in PF-ILD, however, the results (analysis of continuous data) for the L-PF were presented as supplementary information in dossier assessment A20-71.

With its comments [3], the company submitted further documents on the validation of the L-PF as well as analyses on the proportion of patients with a deterioration by ≥ 15% of the scale range (corresponding to an increase by at least 15 points).

The G-BA commissioned IQWiG to assess the validity/suitability of the L-PF in the present therapeutic indication as well as the analysis including the subsequently submitted results on the threshold value ≥ 15% of the scale range, taking into account the information provided in the commenting procedure as well as the information in the dossier.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

Validity of the L-PF

The L-PF is derived from the L-IPF questionnaire developed for idiopathic pulmonary fibrosis (IPF). This questionnaire was developed for patients with IPF and is in turn a further development of the questionnaire A Tool to Assess Quality of Life in IPF (ATAQ-IPF) [4].

According to the company's comments, the L-PF was developed as part of the nintedanib study programme and that psychometric parameters were determined in the INBUILD study available for the assessment. The questionnaire is divided into a symptoms and an impacts module. The symptoms module of the L-PF records the extent of symptoms in relation to physical activities as well as the degree of avoidance of activities due to symptoms within the last 24 hours. Within the symptoms module, the scores of dyspnoea, cough, and fatigue can be calculated. The impacts module, on the other hand, only provides a single score, which reflects the patients' impairments due to symptoms within the last week. The scores range from 0 to 100, with higher scores indicating greater impairment.

The company described in its comments that the INBUILD study recorded and analysed the L-PF in version 1.0, which comprises 44 items.

The documents for the comments include investigations on the content validity as well as the psychometric validation of the instrument for the 44-item version. The psychometric validation was carried out within the framework of the INBUILD study presented for the assessment of the added benefit. Based on the available documents, the validity of the questionnaire in version 1.0 is questionable. For example, the construct validity of the fatigue score could not be shown and none of the scores achieved the preplanned criteria for reliability. The authors of the validation studies themselves describe that there is still a need for further development for version 1.0 of the L-PF with 44 items; in particular, they consider further involvement of patients in the therapeutic indication to be necessary. The validation of a version 2.0 reduced by 9 items, with 35 items, has also already been carried out on the basis of the data from the INBUILD study. For this version 2.0, a deviating scoring algorithm is described and the symptoms score and the impact score can only be combined into a total score with this version. In addition, it is clear from the documents for the company's comments that a further reduction of the items of the impact scale in version 2.0 from 20 to 11 items is considered reasonable.

Analyses submitted for the L-PF

The analyses presented by the company are based on version 1.0 of the L-PF questionnaire, which contains 44 items. As described above, the validity of the 44-item version of the L-PF is questionable on the basis of the available documents. In addition, the analyses of the various response criteria are incomplete. There are no analyses of the fatigue score as a subscore of the symptoms module for the response threshold of 15% of the scale range. Overall, the analyses of the L-PF are therefore not usable for the present assessment. The results are not used for the present benefit assessment, but are presented as a supplementary information in Appendix A.

Since a calculation of a total score for the 44-item version is not provided for according to the documents presented, such a calculation is not presented. Appendix A also contains a supplementary presentation of further response criteria used by the company, which are only available for individual subscores of the L-PF, however. These analyses are also not relevant for the assessment of the added benefit.

Irrespective of this, the observed effects of nintedanib in comparison with the ACT are no more than marginal for the outcome "L-PF", as no further information is available that would allow conclusions to be drawn about the severity of the outcome, and the L-PF would be assigned to the outcome category of non-serious/non-severe symptoms/late complications.

2.1 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of nintedanib from dossier assessment A20-71.

The following Table 1 shows the result of the benefit assessment of nintedanib under consideration of dossier assessment A20-71 and the present addendum.

Table 1: Nintedanib – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with other chronic progressive fibrosing interstitial lung diseases (PF-ILD)	BSC	Indication of minor added benefit[b]

a. Presentation of the respective ACT specified by the G-BA.
b. It is unclear whether the results of the INBUILD study are transferable to other underlying ILD diseases that are underrepresented or not represented in the study.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; ILD: interstitial lung disease; PF-ILD: progressive fibrosing interstitial lung disease

The G-BA decides on the added benefit.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Nintedanib (andere chronische progredient fibrosierende interstitielle Lungenerkrankungen): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A20-71 [online]. 2020 [Accessed: 16.11.2020]. URL: https://www.iqwig.de/download/A20-71_Nintedanib_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

2. Boehringer Ingelheim Pharma. Nintedanib (Ofev): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2020 [Accessed: 16.12.2020]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/578/#dossier.

3. Boehringer Ingelheim Pharma. Stellungnahme zum IQWiG-Bericht Nr. 994: Nintedanib (andere chronische progredient fibrosierende interstitielle Lungenerkrankungen): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A20-71. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/578/#beschluesse in the document "Zusammenfassende Dokumentation"].

4. Boehringer Ingelheim Pharma. Consensus Document on Patient-Reported Outcomes Relevant to Determine Treatment Benefit in Progressive Fibrosing-Interstitial Lung Disease.

Appendix A – Results for the outcome "L-PF"

Table 2: Results for the L-PF (supplementary information) – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC

Study Outcome category Outcome	Nintedanib + BSC		Placebo + BSC		Nintedanib + BSC vs. placebo + BSC
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI][a]; p-value
INBUILD					
Morbidity					
Deterioration by ≥ 15% of the scale range at week 52[b, c]					
Total L-PF symptom score	329	39.72[d] (12.1[e])	323	58.88[d] (18.2[e])	0.67 [0.46; 0.99]; ND
L-PF dyspnoea score	329	68.02[d] (20.7[e])	323	92.53[d] (28.6[e])	0.72 [0.54; 0.97]; ND
L-PF cough score	327	77.74[d] (23.8[e])	320	104.18[d] (32.6[e])	0.72 [0.55; 0.93]; ND
L-PF fatigue score		ND		ND	ND
L-PF impact score	332	49.23[d] (14.8[e])	328	73.18[d] (22.3[e])	0.67 [0.47; 0.95]; ND
Other submitted responder analyses at week 52[b, c]					
L-PF dyspnoea score, deterioration by > 5 points	329	128.41[d] (39.0[e])	323	161.18[d] (49.9[e])	0.78 [0.65; 0.94]; ND
L-PF cough score, deterioration by > 0.5 points	327	138.90[d] (42.5[e])	320	163.96[d] (51.2[e])	0.82 [0.69; 0.97]; ND

a. RR, 95% CI: modified Poisson regression with the adjustment variables baseline value and HRTC pattern. Combining of RR and 95% CI across all imputation data sets using Rubin's rule.
b. Imputation of missing values using multiple imputation.
c. Time at which the last randomized participant had completed the planned treatment duration of 52 weeks.
d. Due to the multiple imputation of missing values, there is usually no whole number of patients with event.
e. Institute's calculation.

BSC: best supportive care; CI: confidence interval; HRCT: high-resolution computed tomography; L-PF: Living with Pulmonary Fibrosis; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; RR: relative risk; vs.: versus