Justification

Gemeinsamer Bundesausschuss

to the Resolution 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

Contents

1. Legal basis

According to Section 35a, paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. Approved therapeutic indications,
2. Medical benefit,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Treatment costs for statutory health insurance funds,
6. Requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA shall pass a resolution on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient nintedanib was listed for the first time on 15 March 2015 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices. Nintedanib for the treatment of idiopathic pulmonary fibrosis is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No 141/2000 of the European Parliament and the Council of 16 December 1999.

At its session on 3 September 2015, the G-BA passed a resolution on the benefit assessment of nintedanib in the present therapeutic indication in accordance with Section 35a SGB V.

If the turnover of the orphan drugs with statutory health insurance at pharmacy retail prices, including value added tax, exceeds € 50 million in the last twelve calendar months, the pharmaceutical company must, within three months of being requested to do so by the Federal Joint Committee, submit evidence in accordance with Section 5, paragraph 1 through 6 demonstrating the additional benefit compared with the appropriate comparator therapy.

The pharmaceutical company was informed about the exceeding of the 50 million Euro turnover limit by letter dated 11 January 2019 and was requested to submit a dossier for the benefit assessment in accordance with 35a SGB V. The pharmaceutical company submitted the final dossier to the G-BA in due time in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 6 VerfO on 10 April 2019.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 15 July 2019, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of nintedanib compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG (IQWiG No. A19-36), the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods was not used in the benefit assessment of nintedanib.

In the light of the above and taking into account the comments received and the oral hearing, the G-BA has arrived at the following assessment:

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

2.1.1 Approved therapeutic indication of nintedanib (Ofev®) in accordance with product information

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

(IPF).

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with idiopathic pulmonary fibrosis

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.

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication according to the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

zu 1. The following medicinal products are approved for the treatment of idiopathic pulmonary fibrosis:

pirfenidone (Esbriet®), methylprednisolone, prednisolone, prednisone

On 2. In the treatment of idiopathic pulmonary fibrosis, measures to support respiratory function (long-term oxygen therapy, pulmonary rehabilitation, physical therapy (in the sense of the Remedies Directive)) can be considered as non-medicinal treatment.

Lung transplantation is a treatment option for patients with idiopathic pulmonary fibrosis. Against the background that idiopathic pulmonary fibrosis is predominantly a disease of old age, that the possibility of lung transplantation is largely determined by patient-individual criteria (including comorbidities), and that the limited availability of suitable donor organs must also be taken into account, with regard to the lung transplantation, a regular therapy option for the patients cannot be assumed according to the present therapeutic indication.

On 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

For the treatment of adult patients with mild to moderate idiopathic pulmonary fibrosis with the active ingredient pirfenidone, an non-quantifiable additional benefit was determined by resolution of 15 March 2012.

On 4. The generally accepted state of medical knowledge for the indication was established by means of a search for guidelines and systematic reviews of clinical studies. For adult patients with idiopathic pulmonary fibrosis, the aforementioned medicinal and non-medicinal therapy options are available. For idiopathic pulmonary fibrosis, the evidence available recommends medicinal therapy with pirfenidone as well as symptomatic therapies to support respiratory function (e.g. through physical therapy). For idiopathic pulmonary fibrosis, treatment is either with pirfenidone (only for patients with mild to moderate idiopathic pulmonary fibrosis according to marketing authorisation) or patient-individual for the relief of symptoms and improvement of the quality of life in the sense of best supportive care (BSC).

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment contract.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of nintedanib is assessed as follows:

For nintedanib for the treatment of idiopathic pulmonary fibrosis in adults, there is a hint for a considerable additional benefit.

Justification:

The three RCTs INPULSIS-1, INPULSIS-2, and TOMORROW, which justified the marketing authorisation, as well as Study 1199.187 were used to assess the additional benefit of nintedanib.

The INPULSIS-1 and INPULSIS-2 studies are randomised, controlled, double-blind Phase III studies with identical study designs and treatment duration of 52 weeks each. In the INPULSIS-1 study, a total of 515 patients were randomized at a ratio of 3:2 to the intervention arm (nintedanib + best supportive care (BSC); N = 309) or the comparator arm (placebo + BSC; N = 206). In the INPULSIS-2 study, a total of 551 patients were assigned to treatment with nintedanib + BSC (N = 331) or placebo + BSC (N = 220) at a ratio of 3:2.

Study 1199.187 is a randomised (ratio of 1:1) controlled, double-blind Phase IIIb study comparing nintedanib vs placebo. It was originally designed to last 52 weeks. As part of a global amendment, the 2-arm blinded phase was shortened to 24 weeks. A total of 113 patients were included in study 1199.187 (nintedanib + BSC; N = 56, placebo + BSC; N = 57).

The TOMORROW study (N = 173) is a 5-arm, randomised (ratio of 1:1:1:1:1) controlled, double-blind Phase II dose-finding study with a study duration of 52 weeks. Of the 5 arms, the placebo (N = 87) and nintedanib 150 mg 2 times daily (N = 86) study arms are included in the present benefit assessment.

The INPULSIS-1, INPULSIS-2, TOMORROW, and 1199.187 each included patients ≥ 40 years with diagnosed idiopathic pulmonary fibrosis and a forced vital capacity (FVC) of at least 50%. However, the actual study patients still had on average about 80% of the target value with regard to the FVC and can therefore be regarded as only slightly restricted in their lung function.

Treatment with intedanib was carried out in all 4 studies according to the product information (150 mg twice daily). When AEs occurred, all studies provided for a dose reduction to 100 mg nintedanib twice daily or a therapy discontinuation. In the two INPULSIS studies as well as in study 1199.187, a re-escalation of the dosage to 150 mg 2 times daily was planned after the AEs had subsided, or a resumption of therapy, preferably with the reduced dosage (100 mg 2 times daily) or the original dosage (150 mg 2 times daily), was possible. In the TOMORROW study, no resumption of therapy or re-escalation of the dosage was planned. However, a relevant influence on the results of the benefit assessment is not assumed because the proportion of patients for whom a re-escalation of the dosage would have been possible is clearly below 20%.

In the INPULSIS-1, INPULSIS-2, and TOMORROW studies, the primary endpoint was the annual decrease in forced vital capacity (FVC). In study 1199.187, the change in the HRCT-QLF score (high-resolution computed tomography – quantitative lung fibrosis score) was the primary endpoint. In addition, endpoints of categories mortality, morbidity, quality of life, and side effects were collected in the NPULSIS-1, INPULSIS-2, TOMORROW, and 1199.187 studies.

The data presented in the dossier show that the patients in all four studies (INPULSIS-1, INPULSIS-2, TOMORROW, and 1199.187) received an adequate medicinal symptomatic therapy in the sense of best supportive care.

In the written statement procedure, the pharmaceutical company submitted a meta-analysis of the INPULSIS-1, INPULSIS-2, TOMORROW and 1199.187 studies, which investigated patient-relevant endpoints (overall survival, FVC, adjudicated acute exacerbations, SGRQ, and adverse events). This analysis also included the study arm of the TOMORROW study with the non-authorisation-compliant dosage of 2 × 100 mg/day nintedanib. Because of the non-authorisation-compliant dosage in this study arm of the TOMORROW study, the analysis is not considered for the present benefit assessment.

Extent and probability of the additional benefit

Mortality

For the endpoint overall survival (time to death regardless of cause) the meta-analysis of the four studies (INPULSIS-1, INPULSIS-2, 1199.187, and TOMORROW) did not reveal any statistically significant difference between nintedanib + BSC and placebo + BSC. Thus, an additional benefit of nintedanib + BSC compared with placebo + BSC is not proven for the endpoint mortality.

Morbidity

Annual decrease of the forced vital capacity (FVC)

In the INPULSIS-1, INPULSIS-2, and TOMORROW studies, the annual decrease in forced vital capacity (FVC) endpoint was assessed as the primary endpoint. In study 1199.187, the endpoint FVC was identified as a secondary endpoint.

For the endpoint annual FVC decrease [ml], the meta-analysis of the INPULSIS-1, INPULSIS-2, and 1199.187 studies revealed a statistically significant advantage of nintedanib + BSC compared with placebo + BSC (MD [95% CI]): 112.42 [79.06; 145.77]; $p < 0.0001$).

The FVC is a surrogate. The data submitted by the pharmaceutical company for surrogate validation for the patient-relevant endpoint mortality are not sufficient to be able to derive an additional benefit for the endpoint mortality base on the FVC because of deficiencies in information retrieval and methodological deficiencies.

Because of the insufficient validation, the presentation of the results for this endpoint is merely supplementary.

Adjudicated acute exacerbations

The endpoint time to first acute exacerbation was surveyed in the INPULSIS-1, INPULSIS-2, TOMORROW and 1199.187 studies. This is defined as the time between randomisation and the occurrence of a significant acute deterioration of the patient's clinical situation. Among other things, this required an increase in dyspnoea and the detection of new pulmonary infiltrates or other abnormalities in the computer tomogram.

The endpoint was identified by the investigator as an adverse event and subsequently adjudicated by a blinded independent committee in the INPULSIS-1, INPULSIS-2, and 1199.187 studies. The committee assigned the acute exacerbations diagnosed by the investigator to the categories "confirmed", "suspected", or "no exacerbation". Adjudicated acute exacerbations were defined as those acute exacerbations that were "confirmed" or "suspected" by the committee. In the TOMORROW study, there was no subsequent adjudication of exacerbation events. Therefore, the TOMORROW study is based on the results of unadjudicated acute exacerbations.

For the endpoint time until the 1st adjudicated acute exacerbation, the meta-analysis of the INPULSIS-1, INPULSIS-2, 1199.187, and TOMORROW studies revealed a statistically significant disadvantage of nintedanib + BSC compared with placebo + BSC (HR [95% CI]: 0.29 [0.11; 0.77]; $p = 0.028$).

For the endpoint adjudicated acute exacerbations, there is a considerable additional benefit of nintedanib + BSC compared with placebo + BSC.

Necessity of oxygen supply

The endpoint necessity of oxygen supply was surveyed in the TOMORROW study only. In the TOMORROW study, no statistically significant difference between the treatment groups could be shown for the endpoint. Thus, the additional benefit for this end point is not proven.

Change of respiratory state – Patient's Global Impression of Change (PGI-C)

In the INPULSIS-1 and INPULSIS-2 studies, the change in respiratory status was assessed by means of the patient reported PGI-C. The survey instrument PGI-C consists of one item. Patients assess the change in their respiratory condition on a 7-step scale from 1 ("much

better") to 7 ("much worse"). Patients who did not report any deterioration of their condition between the start of study and week 52 were evaluated as responders.

In the meta-analysis of the INPULSIS-1 and INPULSIS-2 studies, for the endpoint change in respiratory state (PGI-C), a statistically significant advantage of nintedanib + BSC compared with placebo + BSC was found in the responder analysis (RR [95% CI]: 1.13 [1.01; 1.25]; p = 0.028). Despite the long recall time of 1 year, the results of the PGI-C can be interpreted because it is assumed that the limitations that are due to the long recall time in the study arms are comparable. For the endpoint change of respiratory state (PGI-C), there is a minor additional benefit of nintedanib + BSC compared with placebo + BSC.

The endpoint change of respiratory state (PGI-C) was not surveyed in the TOMORROW and 1199.187 studies.

Endurance by means of the 6 minute walk test (6MWT)

In the 1199.187 and TOMORROW studies, the ability to walk was assessed by means of the 6MWT as a change at the end of each study. In the 1199.187 and TOMORROW studies, the test was performed based on the established standard of the American Thoracic Society (ATS). The test measures the distance in metres that can be covered within six minutes on a hard, flat surface. The measurement of the physical endurance of the patient or the coping with activities of daily life is basically a patient-relevant endpoint. The 6MWT is a standardised and established instrument for determining physical endurance.

In the present situation, the model with random effects is the model of choice for meta-analysis. Because there is no suitable statistical model (neither with the Knapp-Hartung model nor with the DerSimonian-Laird model) with a reasonably interpretable confidence interval for a meta-analysis of the 1199.187 and TOMORROW studies with respect to the endpoint 6MWT, the results are interpreted on the basis of the results of the individual studies.

For the endpoint 6MWT, neither study 1199.187 nor the TOMORROW study showed a statistically significant difference between the treatment groups. An additional benefit is not proven for this endpoint.

In the INPULSIS-1 and INPULSIS-2 studies, the 6MWT was not used.

Coughing by means of Cough and Sputum Assessment Questionnaire (CASA-Q)

In the INPULSIS-1 and INPULSIS-2 studies, the endpoint CASA-Q for recording the intensity of cough symptoms (11 items) was surveyed as a change at the end of study. The CASA-Q was originally developed for patients with chronic obstructive pulmonary disease and chronic bronchitis in order to detect symptoms of cough and sputum. The version of the questionnaire validated for patients with IPF was used in the two INPULSIS studies; 11 items were used for coughing symptoms and coughing burden. A higher score is associated with less symptoms/burden from coughing.

For endpoint coughing (CASA-Q), the meta-analysis of the INPULSIS-1 and INPULSIS-2 studies did not reveal any statistically significant difference between the treatment groups in the coughing symptoms domain or in the coughing burden domain. Thus, for the endpoint coughing (CASA-Q), an additional benefit of nintedanib + BSC compared with placebo + BSC is not proven.

The endpoint coughing (CASA-Q) was not surveyed in the 1199.187 and TOMORROW studies.

Dyspnoea by means of *Shortness of Breath Questionnaire* (SOBQ)

in the INPULSIS-1, INPULSIS-2, and 1199.187 studies, the endpoint dyspnoea (SOBQ) was surveyed as change at end of study. The SOBQ questionnaire measures the severity of dyspnoea in patients using 24 items (21 items: severe shortness of breath in everyday activities, 3 items: extent of restrictions in everyday life). A higher overall score means a higher impairment because of shortness of breath.

In the present situation, the model with random effects is the model of choice for meta-analysis. Because there is no suitable statistical model (neither with the Knapp-Hartung model nor with the DerSimonian-Laird model) with a reasonably interpretable confidence interval for a meta-analysis of the NPULSIS-1, INPULSIS-2, and 1199.187 studies with respect to the endpoint dyspnoea (SOBQ), the results are interpreted on the basis of the results of the individual studies. In the INPULSIS-1, INPULSIS-2, and 1199.187 studies, no statistically significant difference was found between the treatment groups. Thus, an additional benefit for the endpoint dyspnoea (SOBQ) is not proven.

The endpoint dyspnoea (SOBQ) was not surveyed in the TOMORROW study.

Health status (EQ-5D VAS)

In the INPULSIS-1 and INPULSIS-2 studies, the self-assessment of the general health status of the patients was surveyed using the visual analogue scale (VAS) of the EQ-5D questionnaire as a change at week 52 compared with the start of study.

For the endpoint health status (EQ-5D VAS), the meta-analysis of the INPULSIS-1 and INPULSIS-2 studies revealed a statistically significant advantage of nintedanib + BSC compared with placebo + BSC (MD [95% CI]: 3.81 [1.78; 5.85]; $p < 0.001$). The 95% confidence interval of the Hedges' g in this case does not lie fully outside of the irrelevant range of –0.2 to 0.2 so that the clinical relevance of this effect cannot be assessed.

The endpoint health status (EQ-5D VAS) was not collected in the TOMORROW and 1199.187 studies.

<u>Quality of life</u>

St. George's Respiratory Questionnaire (SGRQ)

In the INPULSIS-1, INPULSIS-2, TOMORROW and 1199.187 studies the health-related quality of life was assessed as a change at the end of study using the SGRQ. The SGRQ includes the domains symptoms, activity, and everyday stress. A reduction of the score means an improvement.

Because of the heterogeneity of the results for the endpoint SGRQ in the INPULSIS-1, INPULSIS-2, TOMORROW, and 1199.187 studies, no suitable statistical model with a reasonably interpretable effect estimate and a reasonably interpretable confidence interval is available for a meta-analysis. The interpretation of the results for this endpoint is therefore based on the individual studies.

The responder analyses submitted by the pharmaceutical company were not used in the dossier evaluation of the IQWiG because the response criterion used for this analysis – the MID – was assesses as insufficiently validated. Instead, IQWiG considers the mean difference of the change from start of study to end of study for the sum score of the SGRQ. For the endpoint SGRQ in the INPULSIS-2 (MD [95% CI]: −2.69 [−4.95; −0.43]; $p = 0.020$) and TOMORROW (MD [95% CI]: −6.12 [−10.57; −1.67]; $p = 0.007$) studies, a statistically significant benefit of nintedanib + BSC compared with placebo + BSC is shown. The 95% confidence interval of the Hedges' g in this case does not lie fully outside of the irrelevant range of –0.2 to 0.2 so that the clinical relevance of this effect cannot be assessed.

In the INPULSIS-1 and 1199.187 studies, no statistically significant difference was found between the treatment groups.

Responder analyses based on an MID have general advantages for a clinical evaluation of effects compared with an analysis of mean value differences. However, there is no MID validated for IPF. Because the initial evaluation of nintedanib 2015 used the response criterion determined for COPD and asthma (≤ −4 points) as a substitute, it is also used as a MID in the current benefit assessment procedure.

Because of the heterogeneity of the INPULSIS-1, INPULSIS-2, TOMORROW, and 1199.187 studies, a meta-analytical summary of the results for the responder analysis of the SGRQ (reduction by ≥ 4 points) was dispensed with, and the interpretation of the results is based on the individual studies. For the endpoint SGRQ in the INPULSIS-2 (RR [95% CI]: 1.49 [1.05; 2.11]; p = 0.022) and TOMORROW (RR [95% CI]: 1.81 [1.01; 3.23]; p=0.048), there was a statistically significant benefit of nintedanib+ BSC compared to placebo+ BSC in the responder analysis. In contrast, the effect estimates of the INPULSIS-1 and 1199.187 studies point in the direction of a disadvantage of nintedanib. The effects of the studies are therefore not parallel. In summary, for the endpoint SGRQ, the reduction by ≥ 4 points means neither an advantage nor a disadvantage for nintedanib.

Side effects

For the endpoint serious adverse events (SAE), the meta-analysis of the INPULSIS-1, INPULSIS-2, TOMORROW, and 1199.187 studies did not reveal any statistically significant difference between nintedanib + BSC and placebo + BSC.

For the endpoint discontinuation because of AEs, the meta-analysis of the INPULSIS-1, INPULSIS-2, TOMORROW, and 1199.187 studies showed no statistically significant difference between the treatment groups. A possible double counting of acute exacerbations in the context of adverse events that led to a therapy discontinuation as well as in the context of the endpoint category morbidity reduces the significance of the results on the discontinuations because of AEs.

For the specific AES, for the endpoint gastrointestinal disorders (SOC), the meta-analysis of the INPULSIS-1, INPULSIS-2, TOMORROW, and 1199.187 studies revealed a statistically significant disadvantage of nintedanib + BSC compared with placebo + BSC (RR [95% CI]: 1.92 [1.48; 2.49]; p = 0.004). This effect is mainly caused by the PTs (preferred terms) diarrhoea, nausea, vomiting, and pain in the upper abdomen contained in this SOC for which a statistically significant disadvantage of nintedanib + BSC compared with placebo + BSC was also found. The AEs in the SOC gastrointestinal disorders were, for the most part, not serious.

Overall assessment/conclusion

For the benefit assessment of nintedanib for the treatment of adult patients with idiopathic pulmonary fibrosis, four RCTs were used (INPULSIS-1, INPULSIS-2, 1199.187, and TOMORROW studies). The four studies (INPULSIS-1, INPULSIS-2, 1199.187, and TOMORROW) yielded results on mortality, morbidity, quality of life, and side effects.

For the endpoint overall survival (time to death regardless of cause) the meta-analysis of the four studies (INPULSIS-1, INPULSIS-2, 1199.187, and TOMORROW) did not reveal any statistically significant difference between nintedanib + BSC and placebo + BSC.

In the morbidity category, a statistically significant and clinically relevant advantage was shown in the meta-analyses of the comparison of nintedanib + BSC with placebo + BSC for the endpoints “time to 1st adjudicated acute exacerbation” and “change in respiratory status (PGI-C (responder analysis))”. For the endpoint health status (EQ-5D VAS), the meta-analysis revealed an advantage of nintedanib + BSC compared with placebo + BSC, whereby the clinical relevance of this statistically significant improvement cannot be assessed.

For the endpoints *necessity of* oxygen supply, 6MWT, coughing (CASA-Q), and dyspnoea (SOBQ), no statistically significant difference could be observed between the treatment groups.

In the quality of life category, there is no overall advantage or disadvantage of nintedanib + BSC compared with placebo + BSC for the endpoint SGRQ, either when considering the mean value differences or when considering the SGRQ responders (reduction by ≥ 4 points).

In the side effects category for the specific AEs for the endpoint gastrointestinal disorders (SOC), the meta-analysis of the INPULSIS-1, INPULSIS-2, TOMORROW, and 1199.187 studies revealed a statistically significant disadvantage of nintedanib + BSC compared with placebo + BSC.

The advantage in the morbidity category in the adjudicated acute exacerbation endpoint is classified as considerable and is additionally supported by the clinically relevant advantage in the endpoint "respiratory state variation (PGI-C)" of the morbidity category.

However, the disadvantage of nintedanib identified in the side effects category in the endpoint gastrointestinal disorders does not lead to a downgrading of the extent of the additional benefit in the assessment of the G-BA.

Overall, nintedanib + BSC has a considerable additional benefit compared with placebo + BSC.

Based on the criteria in Section 5, Paragraph 7 of the AM-NutzenV, the G-BA arrived at the following result taking the disease's degree of severity, the written statements, and the oral hearing for adult patients with idiopathic pulmonary fibrosis and determined a considerable additional benefit for the treatment with nintedanib.

Reliability of data (probability of additional benefit)

The assessment of the additional benefit is based on the four RCTs, INPULSIS-1, INPULSIS-2, TOMORROW, and 1199.187.

For the INPULSIS-1, INPULSIS-2, TOMORROW, and 1199.187 studies, the risk of bias is classified as low at the study level.

In the INPULSIS-1, INPULSIS-2, 1199.187, and TOMORROW studies, for the endpoint adjudicated acute exacerbations, only a few events occurred. In the INPULSIS-1 study, the risk of bias for the endpoint adjudicated acute exacerbations is assessed as high because it is questionable whether sufficient blinding of group membership was maintained in the adjudication process. The TOMORROW study was not adjudicated.

The reliability of data is therefore limited for the endpoint adjudicated acute exacerbations.

The patients in the INPULSIS-1, INPULSIS-2, TOMORROW, and 1199.187 studies each had a mild or moderate stage of IPF. Patients with advanced disease were not included in the INPULSIS-1, INPULSIS-2, TOMORROW and 1199.187 studies. It remains unclear whether the results from the INPULSIS-1, INPULSIS-2, TOMORROW, and 1199.187 studies are applicable to all patients with idiopathic pulmonary fibrosis.

In the overall view, the reliability of data provides a hint for an additional benefit.

2.1.4 Summary of the assessment

The present assessment concerns the renewed benefit assessment of the active ingredient nintedanib because the € 50 million Euro sales limit was exceeded. The present assessment refers to the therapeutic indication "treatment of adult patients with idiopathic pulmonary fibrosis".

Nintedanib has received marketing authorisation as an orphan drug.

The G-BA determined pirfenidone (only for patients with mild to moderate idiopathic pulmonary fibrosis according to marketing authorisation) or best supportive care to be an appropriate comparator therapy.

For the benefit assessment of nintedanib for the treatment of adult patients with idiopathic pulmonary fibrosis, four RCTs were used (INPULSIS-1, INPULSIS-2, 1199.187, and TOMORROW studies). These each allow comparative statements to be made for nintedanib + BSC compared with placebo + BSC. The four studies (INPULSIS-1, INPULSIS-2, 1199.187, and TOMORROW) yielded results on mortality, morbidity, quality of life, and side effects.

For the endpoint overall survival (time to death regardless of cause) the meta-analysis of the four studies (INPULSIS-1, INPULSIS-2, 1199.187, and TOMORROW) did not reveal any statistically significant difference between nintedanib + BSC and placebo + BSC.

In the morbidity category, the meta-analysis for the endpoint "time to 1st adjudicated acute exacerbation" reveals a considerable advantage for nintedanib + BSC. A statistically significant and clinically relevant advantage for nintedanib + BSC is also shown for the endpoint "change in respiratory status (PGI-C (responder analysis))". For the endpoint health status (EQ-5D VAS), the meta-analysis revealed an advantage of nintedanib + BSC compared with placebo + BSC, whereby the clinical relevance of this statistically significant improvement cannot be assessed.

In the quality of life category, there is no overall advantage or disadvantage of nintedanib + BSC compared with placebo + BSC, either when considering the mean value differences or when considering the SGRQ responders (reduction by ≥ 4 points).

For the endpoint gastrointestinal disorders (SOC) in the side effects category, the meta-analysis of the INPULSIS-1, INPULSIS-2, TOMORROW, and 1199.187 studies revealed a statistically significant disadvantage of nintedanib + BSC compared with placebo + BSC.

The advantage in the morbidity category in the adjudicated acute exacerbation endpoint is classified as considerable and is additionally supported by the clinically relevant advantage in the endpoint "respiratory state variation (PGI-C)" of the morbidity category. However, the disadvantage of nintedanib identified in the side effects category in the endpoint gastrointestinal disorders does not lead to a downgrading of the extent of the additional benefit in the assessment of the G-BA.

Because of the questionable blinding during adjudication in the INPULSIS-1 study and the lack of adjudication in the TOMORROW study, there is a high risk of bias for the endpoint time to first acute adjudicated exacerbation. Because patients in the advanced stages of the disease were not examined in the studies, there are uncertainties regarding the reliability of data.

The overall conclusion is that for nintedanib for the treatment of adult patients with idiopathic pulmonary fibrosis, there is a hint for a considerable additional benefit of nintedanib compared with the appropriate comparator therapy BSC.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The pharmaceutical company assumes that 69,051,391 adults live in Germany. Starting from the lowest (2.95 per 100,000) or highest (31.6 per 100,000) reported prevalence rate of idiopathic pulmonary fibrosis, the pharmaceutical company assumes a total of 2,037[1]–21,820[2] adult patients with idiopathic pulmonary fibrosis in Germany.

[1] Ohno S, Nakaya T, Bando M, Sugiyama Y. Idiopathic pulmonary fibrosis: results from a Japanese nationwide epidemiological survey using individual clinical records. Respirology 2008; 13 (6): 926–928

[2] Agabiti N, Poretta MA, Bauleo L, Coppola A, Sergiacomi G, Fusco A et al. Idiopathic pulmonary fibrosis (IPF) incidence and prevalence in Italy. Sarcoidosis Vasc Diffuse Lung Dis 2014; 31 (3): 191–197

Taking into account an 86.5 % share of patients covered by statutory health insurance (SHI), the result is 1,763 to 18,881 patients in the target population.

The range given by the pharmaceutical company is subject to uncertainties because the prevalence rates used are based on regions outside Germany. The range mentioned here takes into account uncertainties in the already limited and low quality data basis.

2.3 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: 9 August 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).

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 September 2019).

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Nintedanib	continuous, 2 × daily	365	1	365
Appropriate comparator therapy				
Pirfenidone[3]	continuous, 3 × daily	365	1	365
Best supportive care	different for each individual patient			

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

Usage and consumption:

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Nintedanib	150 mg	300 mg	2 × 150 mg	365	730 × 150 mg
Appropriate comparator therapy					
Pirfenidone[3]	801 mg	2403 mg	3 × 801 mg	365	1095 × 801 mg
Best supportive care	different for each individual patient				

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy retail price level and also deducting the statutory rebates in accordance with Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy wholesale price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Nintedanib	60 SC	€ 2,987.07	€ 1.77	€ 0.00	€ 2,985.30
Appropriate comparator therapy					
Pirfenidone	252 FCT	€ 9,123.87	€ 1.77	€ 517.79	€ 8,604.31
Best supportive care	different for each individual patient				
Abbreviations: FCT = film-coated tablets, SC = soft capsules					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 September 2019

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed and the appropriate comparator therapy according to the product information, no costs for additionally required SHI services had to be taken into account.

3. Bureaucratic costs

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 12 August 2014.

The appropriate comparator therapy established by the G-BA was reviewed. The Subcommittee on Medicinal Products redefined the appropriate comparator therapy at its session on 26 February 2019.

On 10 April 2019, the pharmaceutical company submitted a dossier for the benefit assessment of nintedanib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, Number 6 VerfO.

By letter dated 11 April 2019 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient nintedanib.

The dossier assessment by the IQWiG was submitted to the G-BA on 11 July 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 15 July 2019. The deadline for submitting written statements was 5 August 2019.

The oral hearing was held on 26 August 2019.

By letter dated 26 August 2019, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 13 September 2019.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 24 September 2019, and the proposed resolution was approved.

At its session on 17 October 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	12 August 2014	Determination of the appropriate comparator therapy
Subcommittee Medicinal product	26 February 2019	Redefinition of the appropriate comparator therapy
Working group Section 35a	20 August 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	26 August 2019	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	3 September 2019 17 September 2019	Advice on the dossier evaluation of the Institute for Quality and Efficiency in Health Care (IQWiG), evaluation of the written statement procedure
Subcommittee Medicinal product	24 September 2019	Concluding discussion of the proposed resolution
Plenum	17 October 2019	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 17 October 2019

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

Prof Hecken