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 (New Therapeutic Indication: Other Chronic Fibrosing Interstitial Lung Diseases (ILDs) with a Progressive Phenotype)

of 4 February 2021

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 decides 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 (Ofev) was listed for the first time on 15 March 2015 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

Within the previously approved therapeutic indication, the sales of nintedanib with the statutory health insurance at pharmacy sales prices including value added tax exceeded € 50 million. Proof must therefore be provided for pomalidomide in accordance with Section 5, paragraph 1 through 6 VerfO, and the additional benefit compared with the appropriate comparator therapy must be demonstrated.

On 25 May 2020, the orphan designation of Ofev® was withdrawn from the community register of orphan drugs. Consequently, its status as an orphan drug expired.

On 13 July 2020, Ofev received marketing authorisation for a new therapeutic indication classified as a major variation of Type 2 according to Annex 2, number 2a to Regulation (EC) No. 1234/2008 of the Commission from 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

On 6 August 2020, the pharmaceutical company submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient nintedanib with the new therapeutic indication (other chronic fibrosing interstitial lung diseases with a progressive phenotype) in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

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 16 November 2020, 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, and the written statements presented on this in the written and oral hearing procedure as well as the addendum to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA assessed the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative) according to the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of nintedanib.

In light of the above and taking into account the written statements 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 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)]*.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

- 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.

[1] General Methods, Version 6.0 dated 5 November 2020. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), Cologne.

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 applications 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:

On 1. 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)], the following medicinal products are approved: Methyl prednisolone, prednisolone, prednisone

On 2. In the treatment of chronic fibrosing interstitial lung diseases with a progressive phenotype, 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 generally considered as a therapy option for patients with chronic fibrosing interstitial lung diseases with a progressive phenotype. Against the background that chronic fibrosing interstitial lung disease with a progressive phenotype 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 consideration, 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 active ingredient nintedanib for the treatment of adult patients with idiopathic pulmonary fibrosis, a hint for a considerable additional benefit was determined by the resolution of 17 October 2019.

For the treatment of adult patients with mild to moderate idiopathic pulmonary fibrosis with the active ingredient pirfenidone, a 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. In addition, the scientific medical societies and the Drug Commission of the German Medical Association (AkdÄ) were involved in writing on questions of comparator therapy in the present indication in accordance with Section 35a, paragraph 7 SGB V. For adult patients with other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype, the aforementioned medicinal and non-medicinal therapy options are available. The evidence available recommends symptomatic therapies for chronic fibrosing interstitial lung diseases with a progressive phenotype to support respiratory function (e.g. physical therapy). Other chronic fibrosing interstitial lung diseases with a progressive phenotype are thus treated individually for each patient to alleviate symptoms and improve the quality of life in the sense of best supportive care (BSC).

In clinical practice, immunomodulatory active ingredients are used as possible therapy options for the treatment of patients with chronic PF-ILD in addition to treatment in the sense of a BSC. Immunomodulatory active ingredients are not specifically approved for the present therapeutic indication; however, they may be indicated for treatment in the context of an underlying disease (e.g. rheumatoid arthritis). Insofar as these immunomodulatory active ingredients are used for PF-ILD, there is thus a discrepancy between the medicinal products approved in the indication and those used in care. The proportion of immunomodulatory therapies used in clinical practice is rather low in the present indication because of the lack of marketing authorisation in Germany. After reviewing the evidence available, no general recommendations can be derived for the treatment of chronic PF-ILD itself by immunomodulatory active ingredients.

Overall, the G-BA therefore considers it appropriate to refrain from considering immunomodulatory active ingredients when determining the appropriate comparator therapy.

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:

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

Indication of a minor additional benefit

Justification:

For the assessment of the additional benefit of nintedanib for the treatment of adult patients with other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype, the pivotal INBUILD RCT was used.

The INBUILD study is a randomised, controlled, double-blind Phase III study. In the INBUILD study, a total of 663 patients were randomised at a ratio of 1:1 to the intervention arm (nintedanib + best supportive care (BSC); N = 332) or the comparator arm (placebo + BSC; N = 331).

The INBUILD study included patients with chronic PF-ILD defined by features of diffuse fibrosing lung disease in >10% of lung volume diagnosed by high-resolution computed tomography (HRCT). The patients included had to show deterioration of lung function and respiratory symptoms or progression of fibrotic changes in the lungs assessed by imaging techniques within 24 months prior to screening despite patient-individual therapy. These criteria were defined by a decrease in forced vital capacity (FVC) of ≥ 10% of the target value or an FVC decrease of ≥ 5% to < 10% of the target value in combination with an increase in respiratory symptoms or an FVC decrease of ≥ 5% to < 10% of the target value in combination with an increase in fibrotic changes in chest imaging or an increase in respiratory symptoms as well as fibrotic changes assessed by imaging techniques of the chest. Further inclusion criteria were a diffusing capacity of the lungs for carbon monoxide (DLCO) of 30–80% of the target value and a FVC of ≥ 45% of the target value.

Nintedanib is approved for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype. PF-ILD comprises different underlying diseases, the common feature of which is the occurrence of ILD with a progressive fibrosing phenotype. This basically includes a high number of ILDs as an underlying disease. The study population

of the INBUILD study includes only a sub-set of possible underlying diseases of PF-ILD (e.g. allergic alveolitis, autoimmune-associated ILD, idiopathic non-specific interstitial pneumonia, and unclassifiable idiopathic interstitial pneumonia).

Not all forms of ILD with progressive course are sufficiently represented in the INBUILD study. It is unclear whether certain underlying diseases (e.g. sarcoidosis and patients with exposure-associated lung diseases) are sufficiently represented.

Patients with a diagnosis of idiopathic pulmonary fibrosis (IPF) were excluded from the study. Patients treated with certain immunomodulatory medicinal products (azathioprine, cyclosporin, tacrolimus, rituximab, cyclophosphamide, mycophenolate mofetil, oral corticosteroids of a dose greater than > 20 mg/d) were not included in the study.

The data presented in the dossier show that the patients in the INBUILD study received an adequate medicinal symptomatic therapy in the sense of best supportive care.

In the INBUILD study, treatment with nintedanib was carried out in accordance with the product information (150 mg dosage twice daily).

The treatment duration of the patients in the INBUILD study is 52 weeks. After reaching 52 weeks, patients remained blinded in the study and continued to be treated until the last randomised study participant had completed 52 weeks of treatment.

The primary endpoint in the INBUILD study was the annual decrease in forced vital capacity (FVC). In addition, endpoints in the mortality, morbidity, quality of life, and side effects categories were surveyed in the INBUILD study. The pharmaceutical company submitted evaluations for all patient-relevant endpoints of the INBUILD study at week 52 as well as for the overall study duration (end of study).

The longer observation period is considered reasonable considering the present chronic disease. For evaluations of endpoints in the mortality, morbidity, and side effects categories, the data on the overall study duration are therefore considered in each case. For the evaluations of the patient-reported endpoints (PROs), the 52-week data are used because there is limited validity for the analyses over the overall study duration at individual time points.

Extent and probability of the additional benefit

Mortality

For the endpoint overall survival, there was no statistically significant difference between the treatment groups in the INBUILD study. 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)

The endpoint annual decrease in forced vital capacity (FVC) was surveyed as the primary endpoint at week 52 in the INBUILD study.

For the endpoint annual FVC decline [ml], the INBUILD study showed a statistically significant advantage of nintedanib + BSC compared with placebo + BSC.

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 based 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.

Acute exacerbations or death

Acute exacerbations represent a clinically relevant endpoint and are considered patient-relevant.

In the INBUILD study, both the combined endpoint acute exacerbations or death and acute exacerbations as a separate endpoint were evaluated. For the benefit assessment, the combined endpoint is used because the two components exacerbation or death are considered sufficiently similar in terms of their severity in the present case.

For the combined endpoint acute exacerbation or death, a statistically significant advantage of nintedanib + BSC compared with placebo + BSC was observed at the end of study.

Symptomatology (*King's Brief Interstitial Lung Disease* (K-BILD))

K-BILD is a patient-reported endpoint instrument developed to assess health status specifically in ILD and consists of 15 items spread across three domains (breathlessness and activity, psychological aspects, and thoracic discomfort).

For the endpoint symptomatology surveyed using the K-BILD total score, there was no statistically significant difference between the treatment groups in the INBUILD study.

Health status (EQ-5D VAS)

In the INBUILD study, 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 EQ-5D VAS for the assessment of health status, there was no statistically significant difference between the treatment groups.

Quality of life

In the INBUILD study, the quality of life of adult patients with chronic PF-ILD was assessed using the Living with Pulmonary Fibrosis (L-PF) and Pulmonary Fibrosis Impact on Quality of Life Scale (PF-IQOLS) instruments.

Pulmonary Fibrosis Impact on Quality of Life Scale (PF-IQOLS)

The PF-IQOLS is a generic questionnaire that can record the negative impact of diseases and their treatment on quality of life in chronic diseases. The PF-IQOLS is derived from the Flanagan's Quality of Life Scale (QOLS) and includes the same 16 dimensions. The QOLS was adapted and validated for the first time for the therapeutic indication asthma (A-IQOLS). Each dimension is rated by the patient on a 5-point Likert scale. The PF-IQOLS component score is calculated from the mean value across the individual dimensions.

Because of a lack of information, the validity of this questionnaire cannot be conclusively assessed at present.

Living with Pulmonary Fibrosis (L-PF)

The L-PF questionnaire is derived from the L-IPF, which was developed for patients with IPF and is, in turn, a further development of the "A Tool to Assess Quality of Life in IPF" (ATAQ-IPF) questionnaire. The L-PF comprises 44 items and is divided into the modules symptomatology (23 items) and impact (21 items). In the symptomatology module, both physical activity and its avoidance within the last 24 hours are mapped. Scores for dyspnoea, cough, and fatigue can be calculated from the symptomatology module. On the other hand,

the impact module provides only a score. The total score is formed from these individual scores can have values between 0 and 100; a higher value corresponds to greater impairment.

The evaluations presented by the pharmaceutical company are based on version 1.0 of the L-PF questionnaire, which contains 44 items. This questionnaire is not considered sufficiently validated.

In addition, the evaluations of the various response criteria submitted by the pharmaceutical company in the written statement procedure are incomplete. Evaluations of the fatigue score as a sub-score of the symptomatology module are missing for the response threshold of 15% of the scale range. Overall, the evaluations of the L-PF are therefore not usable for the present assessment.

Side effects

For the endpoint serious adverse events (SAE), there was no statistically significant difference between nintedanib + BSC and placebo + BSC in the INBUILD study.

For the endpoint discontinuation because of AEs, a statistically significant difference to the disadvantage of nintedanib + BSC compared with placebo + BSC was observed in the INBUILD study; this was largely due to diarrhoea. With the exception of diarrhoea, no information is available on the severity of AEs that led to therapy discontinuation.

For specific AEs, a statistically significant disadvantage of nintedanib + BSC compared with placebo + BSC was observed for the endpoint gastrointestinal tract disorders (system organ class (SOC)) in the INBUILD study. This effect is largely due to the PT (preferred term) diarrhoea included in this SOC; for this, a statistically significant disadvantage of nintedanib + BSC compared with placebo + BSC was also found.

In addition, there was a statistically significant disadvantage for the PT reduced appetite in the SOC metabolism and nutrition disorders. For the endpoint reduced appetite, an effect modification by the characteristic age was shown. For patients ≥ 65, there was no statistically significant difference between the treatment arms. For patients < 65, there was a statistically significant disadvantage of nintedanib compared with BSC.

For the endpoint hepatobiliary disorders (SOC), a statistically significant disadvantage of nintedanib + BSC compared with placebo + BSC was observed in the INBUILD study.

Most AEs in the SOC gastrointestinal disorders and PT reduced appetite were not serious. On the other hand, the AEs in the PT diarrhoea (CTCAE ≥ 3) and in the SOC hepatobiliary disorders are classified as serious side effects.

In the side effects category, there are overall negative effects for nintedanib compared with BSC.

Overall assessment

For the benefit assessment of nintedanib for the treatment of adult patients with other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype, the randomised, controlled, double-blind INBUILD Phase III study was submitted. The INBUILD study will provide results on mortality, morbidity, and side effects.

For the endpoint overall survival, there was no statistically significant difference between the treatment groups in the INBUILD study.

In the morbidity category, a statistically significant advantage of nintedanib + BSC compared with placebo + BSC was observed for the combined endpoint acute exacerbation or death.

For the endpoint symptomatology surveyed using the K-BILD total score, there was no statistically significant difference between the treatment groups in the INBUILD study.

For the endpoint EQ-5D VAS for the assessment of health status, there was no statistically significant difference between the treatment groups.

No usable data was submitted in the quality of life category.

In the side effects category, there was no statistically significant difference between nintedanib + BSC and placebo + BSC for the endpoint serious adverse events (SAE) in the INBUILD study.

For the endpoint discontinuation because of AEs, a statistically significant difference to the disadvantage of nintedanib + BSC compared with placebo + BSC was observed in the INBUILD study; this was largely due to diarrhoea.

For specific AEs, a statistically significant disadvantage of nintedanib + BSC compared with placebo + BSC was observed for the endpoint gastrointestinal tract disorders (system organ class (SOC)) in the INBUILD study. This effect is largely due to the PT (preferred term) diarrhoea included in this SOC; for this, a statistically significant disadvantage of nintedanib + BSC compared with placebo + BSC was also found.

In addition, there was a statistically significant disadvantage for the PT reduced appetite in the SOC metabolism and nutrition disorders. For the endpoint reduced appetite, an effect modification by the characteristic age was shown. For patients ≥ 65, there was no statistically significant difference between the treatment arms. For patients < 65, there was a statistically significant disadvantage of nintedanib compared with BSC.

For the endpoint hepatobiliary disorders (SOC), a statistically significant disadvantage of nintedanib + BSC compared with placebo + BSC was observed in the INBUILD study.

In the side effects category, there are overall negative effects for nintedanib compared with BSC.

After weighing the available data, the G-BA concludes that there is a minor additional benefit of nintedanib compared with BSC for the treatment of adult patients with chronic PF-ILD.

Based on the criteria in Section 5, Paragraph 7 of the AM-NutzenV, the G-BA arrived at the following result taking into consideration the severity of the disease, the written statements, and the oral hearing for adult patients with chronic PF-ILD and determined a minor additional benefit for the treatment with nintedanib.

Reliability of data (probability of additional benefit)

The assessment of the additional benefit of nintedanib for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype is based on the INBUILD RCT. For the INBUILD study presented, the risk of bias is classified as low at study level. Similarly, the risk of bias in the results for all endpoints included in the benefit assessment is rated as low.

In the overall view, there is an indication of an additional benefit with regard to the reliability of data.

2.1.4 Summary of the assessment

The present assessment refers to the benefit assessment of a new therapeutic indication for the active ingredient nintedanib (Ofev®). The orphan designation of Ofev® was withdrawn from the community register of orphan drugs. Ofev® also exceeded the € 50 million turnover limit.

Nintedanib is indicated in adults for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype. This resolution relates to the treatment of adult patients with other chronic PF-ILDs *[except idiopathic pulmonary fibrosis (IPF) and interstitial lung disease with systemic sclerosis (SSc-ILD)]*.

Best supportive care (BSC) was determined as an appropriate comparator therapy by the G-BA.

For the benefit assessment of nintedanib for the treatment of adult patients with other chronic PF-ILDs, the randomised, controlled, double-blind INBUILD Phase III study was submitted. The INBUILD study will provide results on mortality, morbidity, and side effects.

For the endpoint overall survival, there was no statistically significant difference between the treatment groups in the INBUILD study.

In the morbidity category, a statistically significant advantage of nintedanib + BSC compared with placebo + BSC was observed for the combined endpoint acute exacerbation or death.

For the endpoint symptomatology surveyed using the K-BILD total score, there was no statistically significant difference between the treatment groups in the INBUILD study.

For the endpoint EQ-5D VAS for the assessment of health status, there was no statistically significant difference between the treatment groups.

No usable data was submitted in the quality of life category.

In the side effects category, there was no statistically significant difference between nintedanib + BSC and placebo + BSC for the endpoint serious adverse events (SAE) in the INBUILD study.

For the endpoint discontinuation because of AEs, a statistically significant difference to the disadvantage of nintedanib + BSC compared with placebo + BSC was observed in the INBUILD study; this was largely due to diarrhoea.

In detail, there were negative effects of nintedanib + BSC compared with placebo + BSC for the specific AEs.

In the side effects category, there are overall negative effects for nintedanib compared with BSC.

After weighing the available data, the G-BA concludes that there is a minor additional benefit of nintedanib compared with BSC for the treatment of adult patients with chronic PF-ILD.

In the overall view, for nintedanib for the treatment of other chronic fibrosing interstitial lung diseases with a progressive phenotype, an indication for a minor additional benefit of nintedanib compared with the appropriate comparator therapy BSC is derived.

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 4,457–11,416 SHI-insured patients in the target population. Overall, the range given by the pharmaceutical company is associated with considerable uncertainties. This is because the prevalence information for ILDs on which the estimate in the dossier is based is suitable for deriving the target population only to a very limited extent because it does not fulfil various criteria of a prevalence in accordance with the IQWiG benefit assessment (among other things, collateral patients are not included and deceased patients are included). In addition, some diagnoses that may be associated with ILD were not considered).

The range mentioned here is mapped despite the uncertainties because of the limited data basis available.

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: 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.

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 January 2021).

For the cost representation, only the dosages of the general case are considered. If the treatment duration is unlimited, initial induction regimens are to be disregarded in the representation of costs. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

Treatment duration:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is different for each individual patient and/or is shorter on average. The time unit “days” is used to calculate the “number of treatments/patient/year”, the time between individual treatments, and the maximum treatment duration if specified in the product information.

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	continuously, 2 × daily	365	1	365
Best supportive care	different for each individual patient			
Appropriate comparator therapy				
Best supportive care	different for each individual patient			

Usage and consumption:

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Nintedanib	150 mg	300 mg	2 × 150 mg	365	730 × 150 mg
Best supportive care	different for each individual patient				
Appropriate comparator therapy					
Best supportive care	different for each individual patient				

Costs:

In order to improve comparability, the costs of the medicinal products were approximated based on the pharmacy sales price level as well as less the statutory rebates according to Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined based on consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on the costs per pack after deduction of the statutory rebates.

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Nintedanib 150 mg	60 WKA	€ 3,264.00	€ 1.77	€ 0.00	€ 3,262.23
Best supportive care	different for each individual patient				
Appropriate comparator therapy					
Best supportive care	different for each individual patient				
Abbreviations: SC = soft capsules					

Pharmaceutical selling price (LAUER-TAXE®) as last revised: 15 January 2021

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 assessed 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

At its session on 21 June 2016, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

The appropriate comparator therapy established by the G-BA was reviewed. At its session on 28 July 2020, the Subcommittee on Medicinal Products redefined the appropriate comparator therapy.

On 6 August 2020, 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 1, sentence 2 VerfO.

By letter dated 7 August 2020 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 12 November 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 16 November 2020. The deadline for submitting written statements was 7 December 2020.

The oral hearing was held on 21 December 2020.

By letter dated 22 December 2020, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by the IQWiG was submitted to the G-BA on 22 January 2021.

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 26 January 2021, and the proposed resolution was approved.

At its session on 4 February 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	21 June 2016	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	28 July 2020	Redefinition of the appropriate comparator therapy
Working group Section 35a	16 December 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	21 December 2020	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	5 January 2021 19 January 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	26 January 2021	Concluding discussion of the draft resolution
Plenum	4 February 2021	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 4 February 2021

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

Prof. Hecken