Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Nintedanib (new therapeutic indication: clinically significant, progressive fibrosing interstitial lung diseases, 6 to < 18 years)

of 7 August 2025

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assess the benefit of all 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 studies the pharmaceutical company have 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 the 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 is 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.

On 12 February 2025, nintedanib received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 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, 12.12.2008, sentence 7).

On 14 February 2025, i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company have submitted a dossier in due time 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

"Ofev is indicated in children and adolescents from 6 to 17 years old for the treatment of clinically significant, progressive fibrosing interstitial lung diseases (ILDs)".

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 May 2025 on the G-BA website (www.g-ba.de), 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 statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA have 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 [1] was not used in the benefit assessment of nintedanib.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA have come to 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 the product information

Ofev is indicated in children and adolescents from 6 to 17 years old for the treatment of clinically significant, progressive fibrosing interstitial lung diseases (ILDs).

Therapeutic indication of the resolution (resolution of 07.08.2025):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Children and adolescents from 6 to 17 years old with clinically significant, progressive fibrosing interstitial lung diseases (ILDs)

Appropriate comparator therapy for nintedanib:

- Best supportive care

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with 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 G-BA 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.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

On 1. In addition to nintedanib, the following active ingredients are approved for the treatment of interstitial lung diseases: Methylprednisolone, prednisolone, prednisone.

On 2. In the treatment of progressive fibrosing interstitial lung diseases, measures to support respiratory function (long-term oxygen therapy, pulmonary rehabilitation, physical therapy (as defined by the Remedies Directive)) and lung transplantation are generally eligible as non-medicinal treatment.

On 3. No resolutions are available for children and adolescents from 6 to 17 years old with clinically significant, progressive fibrosing interstitial lung diseases.

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V". The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

The evidence for the present therapeutic indication is very limited overall. Only guidelines with recommendations for adults could be considered in the evidence synopsis due to a lack of evidence with regard to the relevant population of 6-17-year-olds. The joint written statement of the Society for Paediatric Pulmonology and the Society for Paediatric Rheumatology also points out that recommendations for children and adolescents are very limited due to the lack of suitable randomised controlled clinical studies and are based, among other things, on the transfer of experience from adults to children. All patients receive supportive treatment, including oxygen administration and physiotherapeutic rehabilitation.

Methylprednisolone, prednisolone and prednisone are approved for the treatment of interstitial lung diseases, but these are of secondary importance in PF-ILD (progressive fibrosing interstitial lung diseases). A lung transplant is generally considered as a therapy option for patients with progressive interstitial lung diseases. In view of the fact that the possibility of lung transplantation is largely determined by patient-individual criteria, among others, comorbidities, and the limited availability of suitable donor organs must also be taken into account, lung transplantation cannot be assumed to be a regular therapy option for patients according to the present therapeutic indication.

In the overall analysis, the G-BA determined best supportive care (BSC) as the appropriate comparator therapy for children and adolescents from 6 to 17 years old with clinically significant, progressive fibrosing interstitial lung diseases (ILDs). Best supportive care (BSC) is defined as the therapy that provides the best possible, patient-individual, optimised supportive treatment to alleviate symptoms and improve quality of life. Non-medicinal measures within the meaning of the Remedies Directive or the catalogue of remedies can contribute to alleviation of symptoms.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

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

An additional benefit of nintedanib is not proven for children and adolescents from 6 to 17 years old with clinically significant, progressive fibrosing interstitial lung diseases (ILDs).

Justification:

The pharmaceutical company presented the results of the InPedILD study in the dossier for the benefit assessment. This is a randomised, double-blind, parallel-group study comparing nintedanib with placebo, each in addition to a standard therapy at the doctor's discretion. A total of 39 children and adolescents from 6 to 17 years old with clinically significant, fibrosing interstitial lung disease (ILD) were enrolled in a 2:1 ratio (nintedanib (N = 26) or placebo (N = 13). The stratification factor was the age category (6 to < 12 years vs 12 to ≤ 17 years). Fibrosing disease had to have been detected by a principal investigator using high-resolution computed tomography within the 12 months prior to visit 1, and confirmed by a centralised assessment based on predefined criteria. In addition to visit 2, patients had to have a clinically significant disease characterised by a FAN score ≥ 3 or 1 feature of clinical progression. A further inclusion criterion was an FVC ≥ 25% of the target value collected at visit 2. Following the 24-week double-blind treatment phase of the study, patients in both study arms were able to enter an open-label phase and were treated with nintedanib until the end of the study. The study was conducted from 2020 to 2022 at 43 study sites worldwide (including Europe).

According to the study protocol, a patient-individual, clinically necessary standard therapy was possible in both study arms in addition to the intervention or comparator medication, which could be adjusted during the entire study. In addition, the doctors were able to use individually indicated medicinal products in both study arms at their own discretion, unless these were explicitly excluded according to the study protocol. The pharmaceutical company did not provide specific information in the dossier on the extent and frequency at which supportive measures in the sense of a BSC were used in the study, and referred to the study report. Overall, the supportive therapies permitted in the InPedILD study are considered adequate for the implementation of the appropriate comparator therapy BSC.

Uncertainties of the study

Patients with clinically significant, fibrosing ILD of different aetiologies were enrolled in the InPedILD study. An ad hoc expert group convened by the European Medicines Agency (EMA) during the marketing authorisation procedure considers this pooling to be a suitable solution, in particular due to the similar pathomechanisms and the rarity of the individual underlying diseases. However, it remains unclear whether the results of the InPedILD study are transferable to other underlying ILD diseases that are underrepresented or not represented in the study.

Furthermore, enrolment in the study was not limited to patients with progressive diseases. The patient characteristics show that there was no clinical progression in around 10% of patients at the start of the study. In addition, the information in the study report shows that protocol violations with regard to the inclusion criteria for the presence of fibrosing ILD (approx. 5%) were documented. In principle, a patient may not fulfil more than one of the mentioned criteria. However, the number of patients affected by this overall remains unclear.

Despite the uncertainties described above, it is assumed that the study population of the InPedILD study adequately represents patients with clinically significant, progressive fibrosing interstitial lung diseases.

The patient characteristics also show that around 18% of patients in the InPedILD study had a diagnosis of systemic sclerosis associated ILD (SSc-ILD), which is not covered by the present therapeutic indication. As this is a small percentage of patients, the data of the total population is nevertheless used for the present assessment.

Evidence transfer

In addition to the InPedILD study, the pharmaceutical company used the INBUILD study with adults for the assessment of the additional benefit as part of an evidence transfer. The INBUILD study is a placebo-controlled randomised parallel group study on nintedanib, in which adult patients with chronic progressive fibrosing interstitial lung diseases were examined. The pharmaceutical company justified the need for evidence transfer with the fact that the InPedILD study was designed as a pharmacokinetic and safety study due to the low prevalence in children and adolescents. The marketing authorisation by the European Medicines Agency (EMA) is therefore also justified by the transferability of efficacy and safety from the adult patient population to the paediatric patient population. The pharmaceutical company is of the opinion that the requirements for evidence transfer are also fulfilled for the benefit assessment, as among others, the pathogenesis and clinical picture in adults as well as children and adolescents are sufficiently similar. In addition, the appropriate comparator therapy determined by the G-BA for adults as well as children and adolescents was identical and an additional benefit of nintedanib was identified in adults in the therapeutic indication of other chronic progressive fibrosing interstitial lung diseases.

The derivation of the additional benefit for adults in the therapeutic indication mentioned is mainly based on the endpoint of acute exacerbations or death. In the InPedILD study, only one exacerbation occurred in the intervention arm in children and adolescents from 6 to 17 years old. In addition, the operationalisation of acute exacerbations differs between the InPedILD and INBUILD studies. The German Society for Paediatric Pulmonology and other clinical experts also stated during the written statement procedure that the definition of acute exacerbation of interstitial lung diseases differs between children and adults, but that the underlying concepts are similar.

On the contrary, the evidence transfer accepted by the EMA is based on the treatment effect of nintedanib on forced vital capacity (FVC) in adults. The exploratory efficacy data in paediatric patients were supported by an extrapolation analysis, in which an estimated treatment effect on FVC (percentage of target) over 24 weeks in adults with idiopathic pulmonary fibrosis, other progressive fibrosing interstitial lung diseases and systemic sclerosis associated interstitial lung disease was used to derive the efficacy in paediatric patients with fibrosing interstitial lung diseases. The FVC is a surrogate parameter for which no suitable surrogate validation was submitted by the pharmaceutical company[2]. The FVC endpoint is therefore not patient-relevant per se. There is therefore no suitable extrapolation analysis based on the data of a patient-relevant endpoint that could be considered for the assessment of the additional benefit.

[2] Benefit assessment resolution of the G-BA dated 4 February 2021; Nintedanib (new therapeutic indication: other chronic progressive fibrosing interstitial lung diseases (PF-ILDs))

In addition, the EPAR points out that differences in the pathophysiological processes of pulmonary fibrosis in children and adults have also been identified despite the similarities. In addition, the identification of paediatric patients with fibrosing interstitial lung diseases is a challenge, as none of the clinical, radiological or histological criteria used to diagnose pulmonary fibrosis in adult patients apply to paediatric cases.[3] Even against the background of the heterogeneity of the present patient population with clinically significant, fibrosing interstitial lung diseases of different aetiology, there remains uncertainty regarding the necessary sufficient similarity of the clinical picture between adults and children.

In summary, based on the available data and uncertainties, it is not possible to transfer the results of adults from the INBUILD study to children and adolescents for the assessment of the additional benefit.

Extent and probability of the additional benefit

Mortality

There were no deaths in the course of the study.

Morbidity

Acute exacerbation or death

The pharmaceutical company submitted evaluations on the composite endpoint of acute exacerbations or death. Since an acute exacerbation is a potentially life-threatening event, the two components (exacerbation, death) are estimated to be sufficiently similar in terms of their severity grades.

In the InPedILD study, an acute exacerbation was defined as a significant deterioration of the respiratory tracts over a period of four weeks that necessitated a change in regular treatment. Categorisation required fulfilment of two or more of the following criteria, which were collected as part of the AEs:

- Increase in respiratory rate by ≥ 20%
- Deterioration or development of dyspnoea
- Deterioration or development of abnormalities in the chest radiograph
- Increase in oxygen requirement to achieve the individual baseline saturation (at rest or in case of physical burden)
- Need for additional ventilatory support (in addition to oxygen)
- Deterioration of spirometry in children and adolescents who are able to perform the tests (≥ 10% of the baseline value of vital capacity)
- Reduced tolerance to physical burden

It remains unclear whether all occurring events, such as the increase in respiratory rate or the deterioration in spirometry as laboratory parameters, are directly perceptible by the patient and therefore directly patient-relevant. However, the only exacerbation that occurred in the InPedILD study can be classified as patient-relevant, partly because it led to hospitalisation. The operationalisation of acute exacerbations is therefore considered sufficiently patient-relevant in the present data basis.

[3] Nintedanib European Public Assessment Report (EPAR)

For the endpoint of acute exacerbation or death, there was no statistically significant difference between the treatment groups.

Resilience assessed using the 6-minute walk test (6MWT)

In the study, the 6MWT was performed at baseline (week 0) and at weeks 24 and 52. For the endpoint of (physical) resilience assessed using the 6MWT, the pharmaceutical company submitted continuous evaluations of changes from baseline value up to week 24 in the dossier. In addition, values from patients at week 52 were also included in the model. As the patients switched to the open-label study phase after week 24 and the patients in the comparator arm were also treated with nintedanib in this phase, clear assignment of the effects after week 24 is not possible. In the written statement procedure, the pharmaceutical company stated that the MMRM model estimates the treatment differences exclusively on the basis of the data observed until week 24 although additional data are included in the analyses after week 24. This ensured that subsequent data do not influence the estimate. However, the data is still considered uncertain as a clear assignment is still not possible and the effect estimates can deviate significantly, depending on whether values are included in the MMRM model after a certain point in time or not.
Overall, the evaluations presented by the pharmaceutical company on the endpoint "(physical) resilience", assessed using 6MWT, are therefore unsuitable for the benefit assessment.

Forced vital capacity (FVC)

Being a prognostic parameter in lung function diagnostics, the FVC is also a surrogate parameter. The data presented by the pharmaceutical company for surrogate validation of FVC for mortality are unsuitable, as the effect on the surrogate is not strong enough to derive an effect on overall survival in the present situation. The pharmaceutical company assign the endpoint to morbidity in their present dossier. However, no further information is available as to whether effects on the endpoints in the morbidity category could also be derived from the FVC. Furthermore, the pharmaceutical company did not present any data that would indicate an effect for children and adolescents. The FVC is therefore not used for the present benefit assessment.

Quality of life

To assess health-related quality of life, the pharmaceutical company submitted data from the generic instrument Paediatric Quality of Life Inventory (PedsQL) for assessment of the quality of life of children and adolescents. The questionnaire comprises 23 questions and depicts health-related quality of life across the 4 dimensions of physical functioning, emotional functioning, social functioning and school functioning. Different questionnaires were completed, depending on the age of the patients: PedsQL Young Child Report (< 8 years), PedsQL Child Report (8 to < 13 years) and the PedsQL Report for Teens (≥ 13 years). The survey was conducted at the time of screening, at week 24 and week 52. The pharmaceutical company submitted evaluations of the patient-reported version as well as evaluations of the parent-reported version for all patients. The evaluations of the patient-reported version are used for the benefit assessment due to the preferred direct assessment of health-related quality of life by patients.
Among other things, the pharmaceutical company submitted responder analyses for an improvement or deterioration by ≥ 15 points (scale range 0 to 100) respectively, which were

not pre-specified a priori. Deterioration is considered as suitable operationalisation in the present benefit assessment due to the expected progressive course of the disease in the present therapeutic indication.

For the endpoint of health-related quality of life, assessed using PedsQL, there was no statistically significant difference between the treatment groups.

Side effects

The pharmaceutical company submitted analyses of the overall rates of AEs and SAEs with and without disease-related events respectively. It remains unclear which specific events were considered as disease-related events by the pharmaceutical company. The overall rate of SAEs without disease-related events is considered for the present benefit assessment since the overall rate of SAEs does not include events that can be clearly assigned to the underlying disease.

SAEs and discontinuation due to AEs

For the endpoints of SAEs and discontinuation due to Aes, there was no statistically significant difference between the treatment groups.

Specific AEs

Hepatobiliary disorders (SAEs), gastrointestinal disorders (AEs), diarrhoea (AEs)

For the endpoints of hepatobiliary disorders (SAEs), gastrointestinal disorders (AEs) and diarrhoea (AEs), there was no statistically significant difference between the treatment groups.

Overall assessment

The results of the InPedILD study, comparing nintedanib versus placebo, in each case in addition to standard therapy, are available for the benefit assessment for children and adolescents from 6 to 17 years old with clinically significant, progressive fibrosing interstitial lung diseases. The data allow comparative statements to be made versus the appropriate comparator therapy of best supportive care.

No events occurred in the mortality category during the study.
In the morbidity endpoint category, there was no statistically significant difference for the endpoint "acute exacerbation or death" . No suitable data are available for the endpoint "resilience assessed using the 6-minute walk test (6MWT)". For the category of health-related quality of life assessed using PedsQL, there was no statistically significant difference between the treatment groups. In the category of side effects, there were no statistically significant advantages or disadvantages likewise.

In summary, an additional benefit for children and adolescents from 6 to 17 years old with clinically significant, progressive fibrosing interstitial lung diseases compared with the appropriate comparator therapy of best supportive care is not proven.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient nintedanib. The therapeutic indication assessed here is as follows: "Ofev is indicated in children and adolescents from 6 to 17 years old for the treatment of clinically

significant, progressive fibrosing interstitial lung diseases (ILDs)". The G-BA determined best supportive care as the appropriate comparator therapy.

The results of the InPedILD study, comparing nintedanib versus placebo, in each case in addition to standard therapy, are available for the benefit assessment for children and adolescents from 6 to 17 years old with clinically significant, progressive fibrosing interstitial lung diseases. The data allow comparative statements to be made versus the appropriate comparator therapy.

No events occurred in the mortality category during the study. In the morbidity endpoint category, there was no statistically significant difference for the endpoint "acute exacerbation or death" . No suitable data are available for the endpoint "resilience assessed using the 6-minute walk test (6MWT)". For the category of health-related quality of life assessed using PedsQL, there was no statistically significant difference between the treatment groups. In the category of side effects, there were no statistically significant advantages or disadvantages likewise.

In addition to the InPedILD study, the pharmaceutical company used the INBUILD study with adults for the assessment of the additional benefit as part of an evidence transfer. However, based on the available data and uncertainties, it is not possible to transfer the results from adults to children and adolescents for the assessment of the additional benefit.

In summary, an additional benefit for children and adolescents from 6 to 17 years old with clinically significant, progressive fibrosing interstitial lung diseases compared with the appropriate comparator therapy of best supportive care is not proven.

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 resolution is based on the information provided by the pharmaceutical company.

The stated number of patients in the SHI target population is subject to uncertainty, partly due to the fact that there is no general consensus on the diagnosis of fibrosis in children and adolescents. Furthermore, when determining the percentage of children and adolescents from 6 to 17 years old, it remains unclear whether the percentages were collected from an incident or prevalent patient population and to what extent they are transferable.

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: 3 June 2025):

https://www.ema.europa.eu/en/documents/product-information/ofev-epar-product-information_en.pdf

Treatment should be initiated and monitored only after involvement of a multidisciplinary team (physicians, radiologists, pathologists) experienced in the diagnosis and treatment of fibrosing interstitial lung diseases (ILDs).

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 July 2025).

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 varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

For dosages depending on body weight (BW), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" and "Microcensus 2021 – body measurements of the population" were used as a basis. (average body weight of 6-year-old patients: 23.6 kg; average body weight of 17-year-old patients: 67.2 kg).

Children and adolescents from 6 to 17 years old with clinically significant, progressive fibrosing interstitial lung diseases (ILDs)

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	Continuously, 2 x daily	365.0	1	365.0
Best supportive care	Different from patient to patient			
Appropriate comparator therapy				
Best supportive care	Different from patient to patient			

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 23.0 – 33.4 kg > 57.5 kg	75 mg 150 mg	150 mg 300 mg	6 x 25 mg 2 x 150 mg	365.0 365.0	2,190 x 25 mg 730 x 150 mg
Best supportive care	Different from patient to patient				
Appropriate comparator therapy					
Best supportive care	Different from patient to patient				

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a 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. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Designation of the therapy	Packaging 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 25 mg	120 SC	€ 1,283.63	€ 1.77	€ 0.00	€ 1,281.86
Nintedanib 150 mg	60 SC	€ 2,878.44	€ 1.77	€ 0.00	€ 2,876.67
Best supportive care	Different from patient to patient				
Appropriate comparator therapy					
Best supportive care	Different from patient to patient				
Abbreviations: SC = soft capsules					

LAUER-TAXE® last revised: 15 June 2025

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 the standard expenditure in the course of the treatment are not shown.

Because there are no 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, no costs for additionally required SHI services had to be taken into account.

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA have decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA have decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section

35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain

any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA have decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.
References:
Product information for nintedanib (Ofev); Ofev® soft capsules; last revised: February 2025

3. Bureaucratic costs calculation

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 their session on 25 February 2025, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 14 February 2025, 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 2 VerfO.

By letter dated 17 February 2025 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit 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 May 2025, and the written statement procedure was initiated with publication on the G-BA website on 15 May 2025. The deadline for submitting statements was 5 June 2025.

The oral hearing was held on 23 June 2025.

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 was discussed at the session of the Subcommittee on 29 July 2025, and the proposed draft resolution was approved.

At their session on 7 August 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	25 February 2025	Determination of the appropriate comparator therapy
Working group Section 35a	18 June 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	23 June 2025	Conduct of the oral hearing
Working group Section 35a	1 July 2025 15 July 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	29 July 2025	Concluding discussion of the draft resolution
Plenum	7 August 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 7 August 2025

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

Prof. Hecken