# 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 (Interstitial Lung Disease with Systemic Sclerosis (SSc-ILD))

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 24 September 2019, the pharmaceutical company filed an application to postpone the date for the start of the benefit assessment procedure for nintedanib in the therapeutic indication interstitial lung disease in adults with systemic sclerosis (SSc-ILD) according to Section 35a, paragraph 5b SGB V. At its session on 7 November 2019, the G-BA approved the motion to postpone the relevant date in accordance with Section 35a, paragraph 5b SGB V. The benefit assessment of nintedanib in the therapeutic indication interstitial lung disease in adults with SSc-ILD starts at the same time as the benefit assessment of nintedanib in the therapeutic indication in adults for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype at the latest within four weeks after marketing authorisation of the therapeutic indication in adults for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype in accordance with Chapter 5 Section 8 No. 2 VerfO at the latest six months after the first relevant date (4 weeks after marketing authorisation of the indication interstitial lung disease in adults with SSc-ILD).

On 17 April 2020, nintedanib received a marketing authorisation extension for the therapeutic indication interstitial lung disease in adults with SSc-ILD. The marketing authorisation extension for the therapeutic indication other chronic fibrosing interstitial lung diseases with a progressive phenotype took place on 13 July 2020. Both marketing authorisation extensions are 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 (interstitial lung disease in adults with SSc-ILD) in due time.

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. 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 indicated in adults for the treatment of systemic sclerosis associated interstitial lung disease (SSc-ILD).

**Therapeutic indication of the resolution (resolution of 4 February 2021):**

See approved therapeutic indication

### 2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with systemic sclerosis associated interstitial lung disease (SSc-ILD)

- 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.

[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.

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 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 interstitial lung disease in adults with systemic sclerosis (SSc-ILD), the following medicinal products are approved: Methyl prednisolone, prednisolone, prednisone

On 2. In the treatment of interstitial lung disease in adults with systemic sclerosis (SSc-ILD), 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 therapy option for patients with SSc-ILD. 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:

There are no resolutions in the present therapeutic indication.

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 SSc-ILD, the aforementioned medicinal and non-medicinal therapy options are available. The evidence available recommends symptomatic therapies for SSc-ILD to support respiratory function (e.g. physical therapy). SSc-ILD is 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, the active ingredients cyclophosphamide (CYC) and mycophenolate mofetil (MMF) are used as possible therapy options for a small proportion of patients with SSc-ILD in addition to treatment in the sense of a BSC. However, the

aforementioned immunomodulatory active ingredients are not approved for the present therapeutic indication. 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 for the treatment of SSc-ILD can be derived, especially for MMF.

Overall, the G-BA therefore considers it appropriate to refrain from considering these 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 systemic sclerosis associated interstitial lung disease (SSc-ILD)

An additional benefit is not proven.

Justification:

For the assessment of the additional benefit of nintedanib for the treatment of adult patients with systemic sclerosis associated interstitial lung disease (SSc-ILD), the pivotal SENSCIS RCT was used.

The SENSCIS study is a randomised, controlled, double-blind, multinational Phase III study. In the SENSCIS study, a total of 580 patients were randomised at a ratio of 1:1 to the intervention arm (nintedanib + best supportive care (BSC); N = 290) or the comparator arm (placebo + BSC; N = 290).

For the benefit assessment, the pharmaceutical company submitted evaluations for the SENSCIS study for the entire population as well as for a sub-population. The sub-population includes patients who received mycophenolate mofetil (MMF) as previous therapy or as concomitant treatment within the SENSCIS study (50% of the total population).

In particular, because of the lack of marketing authorisation of MMF for patients with SSc-ILD and on the basis of the evidence available from which no general recommendations for the treatment of SSc-ILD can be derived, MMF was not determined as an appropriate comparator therapy. The population excluding patients with concomitant treatment with mycophenolate mofetil (MMF) is therefore used for the benefit assessment of nintedanib (“non-MMF population”).

The “non-MMF population” comprised 151 patients in the intervention arm (nintedanib + BSC) and 148 patients in the control arm (placebo + BSC).

The SENSCIS study included adults with SSc-ILD. The SSc disease onset should have occurred a maximum of 5 or 7 years before the start of study. The diagnosis of SSc-ILD had to be confirmed according to the American College of Rheumatology or the European League Against Rheumatism criteria and based on a proportion of fibrosis of the lung ≥ 10% in a high-resolution computed tomography scan within the last 12 months before the start of study. Further inclusion criteria were a diffusing capacity of the lungs for carbon monoxide (DLCO) of 30–89% of the target value and a forced vital capacity (FVC) of ≥ 40% of the target value at the start of study.

However, the actual study patients still had on average about 75% of the target value with regard to the FVC and can therefore be regarded as only slightly restricted in their lung function. Overall, the patients included had a rather early stage of SSc-ILD.

In the SENSCIS 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 SENSCIS 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 up to a maximum of 100 weeks.

The primary endpoint in the SENSCIS 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 SENSCIS study. The pharmaceutical company submitted evaluations for all patient-relevant endpoints of the SENSCIS 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 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.

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

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 SENSCIS 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 SENSCIS study.

For the endpoint annual FVC decline [ml], the SENSCIS 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.

*Functional Assessment of Chronic Illness Therapy (FACIT)-dyspnoea*

The FACIT-dyspnoea questionnaire is designed to assess the severity of shortness of breath and its functional impact on various activities of daily living. The FACIT-dyspnoea questionnaire consists of the shortness of breath score and the functional limitations score.

For the shortness of breath score, no statistically significant difference was found between the treatment groups in the SENSCIS study.

For the functional limitations score, there was a statistically significant disadvantage of nintedanib + BSC compared with placebo + BSC. The 95% confidence interval of the Hedges' g in this case does not lie fully outside of the irrelevance range. The clinical relevance of the effect observed in the mean difference can therefore not be assessed.

*Scleroderma Health Assessment Questionnaire (SHAQ)*

The SHAQ questionnaire consists of the Health Assessment Questionnaire-Disability Index (HAQ-DI) and 6 visual analogue scales (VAS) to assess scleroderma-specific disease symptomatology. The HAQ-DI patient questionnaire assesses the physical functional status, including activities of daily living. It consists of 8 domains (dressing/undressing, personal hygiene, standing up, eating, walking, hygiene, reachability of objects, gripping, and general daily activities). The items for these 8 domains are each answered on a 4-point Likert scale. A value of 0 corresponds to "without difficulty" and a value of 3 to "unable to perform". The functional status is calculated using the mean values of the individual domains.

For the HAQ-DI scales, Pain VAS, Respiratory problems VAS, and Disease severity overall VAS, there was no statistically significant difference between the treatment groups in the SENSCIS study.

The Intestinal problems VAS records the impairment of daily activities because of intestinal problems over the course of the last seven days. The values range from 0 (no impairment) to 10 (very strong impairment). In the SENSCIS study, there was a statistically significant and clinically relevant disadvantage of nintedanib + BSC compared with placebo + BSC for the Intestinal problems VAS.

For the Raynaud's syndrome VAS and the Digital ulcerations VAS, there was a statistically significant disadvantage of nintedanib + BSC compared with placebo + BSC. The 95% confidence interval of the Hedges' g in this case does not lie fully outside of the irrelevance range. The clinical relevance of the effect observed in the mean difference can therefore not be assessed.

*Health status (EQ-5D VAS)*

In the SENSCIS 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.

*Health status (Patient Global Impression of Health VAS)*

In the SENSCIS study, the patients' self-assessment of their general health status was recorded using the Patient Global Impression of Health VAS as the change at week 52 compared with the start of study. For the endpoint Patient Global Impression of Health VAS, no statistically significant difference was found between the treatment groups.

<u>Quality of life</u>

*St. George's Respiratory Questionnaire (SGRQ)*

In the SENSCIS study, health-related quality of life was surveyed using the SGRQ as a change at the end of study. The SGRQ includes the domains symptoms, activity, and everyday stress. A reduction of the score means an improvement.

The responder analyses submitted by the pharmaceutical company were not used in the dossier assessment of the IQWiG because the response criterion used for this analysis – the MID – was assesses as insufficiently validated. Instead, the IQWiG considers the mean difference of the change from the start of study to the end of study for the component score of the SGRQ.

For the total score of the SGRQ, there was no statistically significant difference between the treatment groups.

Regardless of whether responder analyses based on a response criterion (reduction ≥ 4 points) can be considered in this indication, the study shows no statistically significant difference between the treatment groups for the endpoint SGRQ.

Side effects

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

For the endpoints metabolic and nutrition disorders (SOC) and vascular disorders (SOC), a statistically significant disadvantage of nintedanib + BSC compared with placebo + BSC was found in each case in the SENSCIS study. However, it is questionable whether the negative effect in the SOC vascular disorders belongs to the category of side effects or possibly reflects symptoms of the disease SSc-ILD.

Most AEs in the SOCs gastrointestinal disorders, metabolic and nutritional disorders, and vascular disorders were not serious. On the other hand, the AEs in the PT diarrhoea are classified as serious side effects (CTCAE ≥ 3).

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

Overall assessment

For the benefit assessment of nintedanib for the treatment of interstitial lung disease in adults with systemic sclerosis (SSc-ILD), the randomised, controlled, double-blind, multinational SENSCIS phase III study was submitted. Results on mortality, morbidity, quality of life, and side effects are available from the SENSCIS study.

In particular, because of the lack of marketing authorisation of MMF for patients with SSc-ILD and on the basis of the evidence available from which no general recommendations for the treatment of SSc-ILD can be derived, MMF was not determined as an appropriate comparator therapy. The population excluding patients with concomitant treatment with mycophenolate mofetil (MMF) is therefore used for the benefit assessment of nintedanib (“non-MMF population”).

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

In the morbidity category, no statistically significant difference was found between the treatment groups for the endpoint FACIT-dyspnoea in the shortness of breath score in the SENSCIS study. For the functional limitations score of FACIT-dyspnoea, nintedanib + BSC showed a statistically significant disadvantage compared with placebo + BSC, although the clinical relevance of this statistically significant deterioration can not be assessed.

For the HAQ-DI scales, Pain VAS, Respiratory problems VAS, and Disease severity overall VAS of the SHAQ, there was no statistically significant difference between the treatment groups in the SENSCIS study.

In the SENSCIS study, there was a statistically significant and clinically relevant disadvantage of nintedanib + BSC compared with placebo + BSC for the intestinal problems VAS of SHAQ.

For the Raynaud's syndrome VAS and digital ulcerations VAS of the SHAQ, there was a statistically significant disadvantage of nintedanib + BSC compared with placebo + BSC, although the clinical relevance of this statistically significant deterioration can not be assessed in each case.

For the endpoints EQ-5D VAS and Patient Global Impression of Health VAS for the assessment of health status, there was no statistically significant difference between the treatment groups.

In the quality of life category, no statistically significant difference was found between the treatment groups for the endpoint SGRQ.

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 SENSCIS 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 SENSCIS 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 SENSCIS 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. For the endpoints metabolic and nutrition disorders (SOC) and vascular disorders (SOC), a statistically significant disadvantage of nintedanib + BSC compared with placebo + BSC was found in each case in the SENSCIS study.

In the overall view, there are negative effects for nintedanib compared with BSC in the endpoints Intestinal problems VAS of the SHAQ and discontinuation because of AE. Based on the gastrointestinal side effects reported for nintedanib, it can be assumed that the negative effect of the morbidity category observed in the Intestinal problems VAS is also at least partly due to the side effects of nintedanib and not solely due to changes in disease-specific symptomatology.

In view of the positive approval decision and after weighing the available data, the G-BA concludes that, in the present case, the disadvantages of nintedanib + BSC compared with placebo + BSC identified do not lead to the derivation of a lower benefit. In the overall assessment, the G-BA therefore concludes that an additional benefit of nintedanib compared with BSC for the treatment of adult patients with SSc-ILD is not proven.

### 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 systemic sclerosis associated interstitial lung disease (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 interstitial lung disease in adults with systemic sclerosis (SSc-ILD), the randomised, controlled, double-blind, multinational SENSCIS phase III study was submitted. Results on mortality, morbidity, quality of life, and side effects are available from the SENSCIS study.

In particular, because of the lack of marketing authorisation of MMF for patients with SSc-ILD and on the basis of the evidence available from which no general recommendations for the treatment of SSc-ILD can be derived, MMF was not determined as an appropriate comparator therapy. The population excluding patients with concomitant treatment with mycophenolate mofetil (MMF) is therefore used for the benefit assessment of nintedanib ("non-MMF population").

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

In the morbidity category, no statistically significant difference was found between the treatment groups for the endpoint FACIT-dyspnoea in the shortness of breath score in the SENSCIS study. For the functional limitations score of FACIT-dyspnoea, nintedanib + BSC showed a statistically significant disadvantage compared with placebo + BSC, although the clinical relevance of this statistically significant deterioration can not be assessed.

For the HAQ-DI scales, Pain VAS, Respiratory problems VAS, and Disease severity overall VAS of the SHAQ, there was no statistically significant difference between the treatment groups in the SENSCIS study.

In the SENSCIS study, there was a statistically significant and clinically relevant disadvantage of nintedanib + BSC compared with placebo + BSC for the Intestinal problems VAS of SHAQ.

For the Raynaud's syndrome VAS and Digital ulcerations VAS of the SHAQ, there was a statistically significant disadvantage of nintedanib + BSC compared with placebo + BSC, although the clinical relevance of this statistically significant deterioration can not be assessed in each case.

For the endpoints EQ-5D VAS and Patient Global Impression of Health VAS for the assessment of health status, there was no statistically significant difference between the treatment groups.

In the quality of life category, no statistically significant difference was found between the treatment groups for the endpoint SGRQ.

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 SENSCIS 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 SENSCIS 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 overall view, there are negative effects for nintedanib compared with BSC in the endpoints Intestinal problems VAS of the SHAQ and discontinuation because of AE. Based on the gastrointestinal side effects reported for nintedanib, it can be assumed that the negative effect of the morbidity category observed in the Intestinal problems VAS is also at least partly due to the side effects of nintedanib and not solely due to changes in disease-specific symptomatology.

In view of the positive approval decision and after weighing the available data, the G-BA concludes that, in the present case, the disadvantages of nintedanib + BSC compared with placebo + BSC identified do not lead to the derivation of a lower benefit. In the overall assessment, the G-BA therefore concludes that an additional benefit of nintedanib compared with BSC for the treatment of adult patients with SSc-ILD 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 pharmaceutical company assumes that 69,421,785 adults live in Germany. Taking into consideration that 87.7% of patients are insured by SHI, this results in 60,860,787 adults in SHI.

Based on the average prevalence of 25.97 per 100,000[2] as the baseline value as well as the lowest (40 per 1000,000)[3] or highest (35 per 100,000)[4] reported prevalence rate of SSc, a total of 15,806 (2,434 - 21,301) adult patients with SSc in SHI in Germany is assumed by the pharmaceutical company.

To calculate the ratio of patients with ILD to those with SSc, the pharmaceutical company uses the average prevalence as the baseline value of 30.90%[5] and the low lower limit of 9.45% (patients with ILD fibrosis of > 10%)[6] or highest upper limit of 50.15% (patients with ILD fibrosis regardless of fibrosis grade)[6]. This results in a total of 4,886 (230–10,683) adults with SSc-ILD in SHI.

The range given by the pharmaceutical company is subject to uncertainties because the prevalence rates used are underestimated overall. In the overall view, it is assumed that the number of patients in the SHI target population is in the upper end of the range stated by the pharmaceutical company.

## 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

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[2] Schulz M, Wandrey M, Hering R, Schulz M, Bätzing-Feigenbaum J, Prävalenz seltener Erkrankungen in der ambulanten Versorgung in Deutschland im Zeitraum von 2008 bis 2011 [Prevalence of rare diseases in outpatient care in Germany from 2008 to 2011]. 2015

[3] Deutsches Netzwerk für Systemische Sklerodermie [German Network for Systemic Scleroderma]. Patient information. URL: http://sklerodermie.info/patienteninformation/.

[4] European Medicines Agency. Public summary of opinion on orphan designation Paquinimod for the treatment of systemic sclerosis. 2011. URL: https://www.ema.europa.eu/en/documents/orphan-designation/eu/3/10/836-public-summary- opinion-orphan-designation-paquinimod-treatment-systemic-sclerosis_en.pdf.

[5] Kreuter M, Bonella F, Blank N, Siegert E, Henes J, Worm M et al. Predictors for the development of systemic sclerosis associated interstitial lung disease (SSc-ILD) -data from the German SSc-network. Presented at the American Thoracic Society Conference 2019.

[6] Hoffmann-Vold AM, Fretheim H, Halse AK, Seip M, Bitter H, Wallenius M et al. Tracking impact of interstitial lung disease in systemic sclerosis in a complete nationwide cohort. Am J Respir Crit Care Med 2019; 200(10): 1258–1266.

Treatment with nintedanib should be initiated and monitored only by specialists who are experienced in the treatment of patients with interstitial lung disease with systemic sclerosis (SSc-ILD).

## 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 | Annual average consumption by potency |
|---|---|---|---|---|---|
| Medicinal product to be assessed | | | | | |
| Nintedanib | 150 mg | 300 mg | 2 × 150 mg | 365 | 730 × 150 mg |

| Designation of the therapy | Dosage/ application | Dose/patient/treatment days | Consumption by potency/treatment day | Treatment days/ patient/ year | Annual average consumption by potency |
|---|---|---|---|---|---|
| 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 28 July 2020, the Subcommittee on Medicinal Products determined 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.

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 | 28 July 2020 | Determination of the appropriate comparator therapy |
| Working group Section 35a | 16 December 2020 | Information on written statements received; preparation of the oral hearing |
| Subcommittee on | 21 December 2020 | Conduct of the oral hearing |

| | | |
|---|---|---|
| Medicinal Products | | |
| Working group Section 35a | 5 January 2021<br>19 January 2021 | Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure |
| Subcommittee on<br>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