Nintedanib (systemic sclerosis-associated interstitial lung disease, 6 to 17 years)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50679 Köln
Germany

Phone:+49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

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Medical and scientific advice

No advisor on medical and scientific questions was involved in the present dossier assessment.

Patient and family involvement

No patients or families were involved in the present dossier assessment.

IQWiG employees involved in the dossier assessment

- Anja Reinartz
- Lukas Gockel
- Tatjana Hermanns
- Stefan Kobza
- Mattea Patt
- Daniela Preukschat
- Min Ripoll
- Dominik Schierbaum
- Veronika Schneck

Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BSC	best supportive care
FVC	forced vital capacity
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SSc-ILD	systemic sclerosis-associated interstitial lung disease

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug nintedanib. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 17 February 2025.

Research question

The aim of this report is to assess the added benefit of nintedanib in comparison with best supportive care (BSC) as the appropriate comparator therapy (ACT) in children and adolescents aged 6 to 17 years with systemic sclerosis-associated interstitial lung disease (SSc-ILD).

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of nintedanib

Therapeutic indication	**ACT**[a]
Children and adolescents from 6 to 17 years old with systemic sclerosis-associated interstitial lung disease (SSc-ILD)	BSC[b, c]

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
c. Comments from the G-BA:
- Methylprednisolone, prednisolone and prednisone are approved for the treatment of interstitial lung disease, but are of secondary importance in SSc-ILD. Non-drug interventions as outlined in the German Remedies Directive or the Remedies Catalogue can help to alleviate symptoms. The type and scope of the interventions used must be documented.
- In principle, a lung transplant is a treatment option that can be considered for patients with SSc-ILD. In view of the fact that the possibility of a lung transplantation is largely determined by patient-specific criteria, including comorbidities, and that the limited availability of suitable donor organs must also be taken into account, lung transplantation cannot be assumed to be a standard treatment option for patients in the given therapeutic indication. Nevertheless, patients in studies used for the benefit assessment could also be included in the event of a lung transplantation during the course of the study, in the sense of a permitted treatment switch. Such a treatment switch may correspond to the actual health care setting. Observation of these patients should be continued even after completion of the experimental or comparator intervention of the study.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; SSc-ILD: systemic sclerosis-associated interstitial lung disease

Concurring with the G-BA, the company determined BSC as the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of the added benefit.

Results

The company stated in Module 4 A that the study InPedILD was identified. It explained that the InPedILD study only included 7 children and adolescents with SSc-ILD and that, due to the small number of children and adolescents, it was not possible to derive any results on the medical benefit or added medical benefit.

The InPedILD study is a randomized, double-blind, parallel-group study comparing nintedanib with placebo, each in addition to standard of care at the physician's discretion. The study was conducted from 2020 to 2022. Following the 24-week double-blind phase of the study, patients from both study arms were able to enter an open-label phase and were treated with nintedanib until the end of the study. Children and adolescents aged 6 to 17 years with clinically significant fibrosing interstitial lung disease were enrolled.

The InPedILD study included a total of 39 patients with clinically significant fibrosing interstitial lung disease of different aetiology who were randomly allocated in a 2:1 ratio to treatment with nintedanib (N = 26) or with placebo (N = 13). The subpopulation with SSc-ILD in the InPedILD study included a total of 7 patients, 4 in the intervention arm and 3 in the control arm. The stratification factor was the age category (6 to < 12 years versus 12 to ≤ 17 years).

The company presented the results for the total population of the study in Module 4 A and referred to Appendix 4-G for study data on patients with SSc-ILD. The company therefore did not prepare any data on the given research question in Module 4 A; only isolated descriptive data on study results can be found in Appendix 4-G. Thus, no suitable data were available to answer the given research question. Regardless of this, it was not assumed on the basis of the study documents that it would be possible to observe relevant effects in this small subpopulation of patients with SSc-ILD.

Results on added benefit

In its dossier, the company presented no suitable data for the assessment of the added benefit of nintedanib + BSC in comparison with the ACT BSC for patients aged 6 to 17 years with SSc-ILD. However, based on the study documents, it cannot be assumed that relevant effects could be observed in the subpopulation of patients with SSc-ILD in the InPedILD study. There was no hint of an added benefit of nintedanib + BSC in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 shows a summary of probability and extent of the added benefit of nintedanib.

Table 3: Nintedanib – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Children and adolescents from 6 to 17 years old with systemic sclerosis-associated interstitial lung disease (SSc-ILD)	BSC[b, c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
c. Comments from the G-BA:
- Methylprednisolone, prednisolone and prednisone are approved for the treatment of interstitial lung disease, but are of secondary importance in SSc-ILD. Non-drug interventions as outlined in the German Remedies Directive or the Remedies Catalogue can help to alleviate symptoms. The type and scope of the interventions used must be documented.
- In principle, a lung transplant is a treatment option that can be considered for patients with SSc-ILD. In view of the fact that the possibility of a lung transplantation is largely determined by patient-specific criteria, including comorbidities, and that the limited availability of suitable donor organs must also be taken into account, lung transplantation cannot be assumed to be a standard treatment option for patients in the given therapeutic indication. Nevertheless, patients in studies used for the benefit assessment could also be included in the event of a lung transplantation during the course of the study, in the sense of a permitted treatment switch. Such a treatment switch may correspond to the actual health care setting. Observation of these patients should be continued even after completion of the experimental or comparator intervention of the study.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; SSc-ILD: systemic sclerosis-associated interstitial lung disease

The G-BA decides on the added benefit.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

I 2 Research question

The aim of this report is to assess the added benefit of nintedanib in comparison with BSC as the ACT in children and adolescents aged 6 to 17 years with SSc-ILD.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of nintedanib

Therapeutic indication	**ACT**[a]
Children and adolescents from 6 to 17 years old with systemic sclerosis-associated interstitial lung disease (SSc-ILD)	BSC[b, c]

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
c. Comments from the G-BA:
- Methylprednisolone, prednisolone and prednisone are approved for the treatment of interstitial lung disease, but are of secondary importance in SSc-ILD. Non-drug interventions as outlined in the German Remedies Directive or the Remedies Catalogue can help to alleviate symptoms. The type and scope of the interventions used must be documented.
- In principle, a lung transplant is a treatment option that can be considered for patients with SSc-ILD. In view of the fact that the possibility of a lung transplantation is largely determined by patient-specific criteria, including comorbidities, and that the limited availability of suitable donor organs must also be taken into account, lung transplantation cannot be assumed to be a standard treatment option for patients in the given therapeutic indication. Nevertheless, patients in studies used for the benefit assessment could also be included in the event of a lung transplantation during the course of the study, in the sense of a permitted treatment switch. Such a treatment switch may correspond to the actual health care setting. Observation of these patients should be continued even after completion of the experimental or comparator intervention of the study.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; SSc-ILD: systemic sclerosis-associated interstitial lung disease

Concurring with the G-BA, the company determined BSC as the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

I 3 Information retrieval and study pool

The study pool for the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- Study list on nintedanib (status: 2 December 2024)
- Bibliographical literature search on nintedanib (last search on 2 December 2024)
- Search of trial registries/trial results databases for studies on nintedanib (last search on 2 December 2024)
- Search on the G-BA website for nintedanib (last search on 2 December 2024)

To check the completeness of the study pool:

- Search in trial registries for studies on nintedanib (last search on 11 March 2025); for search strategies, see I Appendix A of the full dossier assessment

The company stated in Module 4 A that the study InPedILD [3,4] was identified. It explained that the InPedILD study only included 7 children and adolescents with SSc-ILD and that, due to the small number of children and adolescents, it was not possible to derive any results on the medical benefit or added medical benefit.

The InPedILD study is a randomized, double-blind, parallel-group study comparing nintedanib with placebo, each in addition to standard of care at the physician's discretion. The study was conducted from 2020 to 2022. Following the 24-week double-blind phase of the study, patients from both study arms were able to enter an open-label phase and were treated with nintedanib until the end of the study. Children and adolescents aged 6 to 17 years with clinically significant fibrosing interstitial lung disease were enrolled. Fibrosing disease had to have been established within 12 months prior to Visit 1 by an investigator using high-resolution computed tomography, and confirmed by a central review based on predefined criteria. In addition, patients had to have clinically significant disease at Visit 2, characterized by a Fan score ≥ 3 or one characteristic of clinical progression. The criteria for clinical progression over time were defined as a ≥ 10% decline in forced vital capacity (FVC) predicted, a ≥ 5% to <10 % decline in FVC predicted accompanied by worsening symptoms, increased fibrosis on high-resolution computed tomography, or other measures of clinical worsening attributed to progressive disease (e.g. increased oxygen requirement, decreased diffusion capacity). Another inclusion criterion was an FVC of ≥ 25% predicted, recorded at Visit 2.

The InPedILD study included a total of 39 patients with clinically significant fibrosing interstitial lung disease of different aetiology who were randomly allocated in a 2:1 ratio to treatment with nintedanib (N = 26) or with placebo (N = 13). The subpopulation with SSc-ILD in the

InPedILD study included a total of 7 patients, 4 in the intervention arm and 3 in the control arm. The stratification factor was the age category (6 to < 12 years versus 12 to ≤ 17 years). All patients who were treated with the study medication until the end of the study were able to switch to the single-arm, open-label extension study InPedILD-ON [5].

The company presented the results for the total population of the study in Module 4 A and referred to Appendix 4-G for study data on patients with SSc-ILD. The company therefore did not prepare any data on the given research question in Module 4 A; only isolated descriptive data on study results can be found in Appendix 4-G. Thus, no suitable data were available to answer the given research question. Regardless of this, it was not assumed on the basis of the study documents that it would be possible to observe relevant effects in this small subpopulation of patients with SSc-ILD.

The review of the completeness of the study pool did not identify any additional studies.

I 4 Results on added benefit

In its dossier, the company presented no suitable data for the assessment of the added benefit of nintedanib + BSC in comparison with the ACT BSC for patients aged 6 to 17 years with SSc-ILD. However, based on the study documents, it cannot be assumed that relevant effects could be observed in the subpopulation of patients with SSc-ILD in the InPedILD study. There was no hint of an added benefit of nintedanib + BSC in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of nintedanib in comparison with the ACT is summarized in Table 5.

Table 5: Nintedanib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Children and adolescents from 6 to 17 years old with systemic sclerosis-associated interstitial lung disease (SSc-ILD)	BSC[b, c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
c. Comments from the G-BA:
- Methylprednisolone, prednisolone and prednisone are approved for the treatment of interstitial lung disease, but are of secondary importance in SSc-ILD. Non-drug interventions as outlined in the German Remedies Directive or the Remedies Catalogue can help to alleviate symptoms. The type and scope of the interventions used must be documented.
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ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; SSc-ILD: systemic sclerosis-associated interstitial lung disease

The assessment described above concurs with that by the company.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a25-29.html.