# Recommendation No. 126/2021 of 23 November 2021 of the President of the Agency for Health Technology Assessment and Tariff System on the reimbursement of Ofev (nintedanib) under the drug programme "Nintedanib treatment of systemic sclerosis-associated interstitial lung disease (ICD-10 M34+J99.1)"

**The President of the Agency** recommends the reimbursement of Ofev (nintedanib) under the drug programme "Nintedanib treatment of systemic sclerosis-associated interstitial lung disease (ICD-10 M34+J99.1)" in the existing limit group and dispensing it free of charge provided that [information protected as a trade secret] and introducing an additional risk-sharing scheme, which will guarantee the reimbursement of treatment costs in patients in whom the decrease in forced vital capacity was not inhibited significantly.

## Grounds for the recommendation

The results of the clinical analysis based on the randomised SENSCIS trial together with its extension SENSCIS-ON, which compared the efficacy of nintedanib (NIN) in combination with standard of care (SoC) with the efficacy of SoC + placebo (PLC) in the treatment of systemic sclerosis-associated interstitial lung disease.

The average decrease of forced vital capacity (FVC) after 52 weeks in the group treated with NIN + SoC was statistically significantly lower than in patients using PLC+SoC. The average difference between the two groups was 41.0 ml/year. Significant statistical superiority was achieved by nintedanib therapy for the endpoints of changes in FVC greater than 5% – regarding both dependent and initial values. The risk of a 5% decrease in ideal value in FVC was 28% lower in the intervention group than in the placebo group, the risk of a 5% decrease in the initial value was 24% lower. In addition, NIN + SoC treatment was associated with a 35% lower risk of the FVC decrease above 10% of the normal value or death, and also with a 43% lower risk of the FVC decrease in respect of initial values by ≥10% of the normal value, or the FVC decrease in respect to initial values by ≥5% to <10% of the normal value, and a decrease in the diffusing capacity for carbon monoxide (DLCO) in respect to initial values by ≥15% of the normal value or death.

Values for minimal clinically important differences (improvement, stabilisation or deterioration) were estimated based on Scleroderma Lung Studies I and II (Tashkin 2016) and were anchored in the SF-36 questionnaire. Statistical significance was not achieved only in the stabilisation endpoint. The use of NIN was associated with a more than 1.5-fold greater chance of improving FVC by at least 3% and

with a 23% lower risk of deteriorating FVC by at least 3.3% than the use of PLC.

The SENSCIS-ON extension trial demonstrated that the average change in FVC in the population that started treatment with NIN is similar to the absolute average change in forced vital capacity in respect to initial values in patients who received NIN for 52 weeks in the randomised phase of the trial (-51.3 ml vs. -54.6 ml). In the PLC group of the SENSCIS trial, the rate of deterioration of the pulmonary function was much higher - the average absolute change in FVC in respect to initial values was -101 ml.

The main limitation of the applicant's clinical analysis is the use of FVC as the primary endpoint, instead of overall survival. This choice was justified based on the FDA decision and the use of this surrogate in other studies for this type of disease.

The above conclusion on the efficacy of the proposed technology is consistent with Opinion of the President of the Agency No. 131/2020 of 12 October 2020 in terms of the use of nintedanib in the treatment of pulmonary fibrosis associated with systemic sclerosis (ICD-10: J84.1) under the emergency access to drug health technologies. The opinion indicates that, taking into account the potential benefits of the treatment and the fact that the currently available treatment options have been exhausted in the assessed population, it is reasonable to reimburse nintedanib therapy in the assessed population.

According to the applicant's estimates, from the NHF perspective, the use of NIN + SoC therapy instead of SoC is [information protected as a trade secret]. The estimated ICUR to compare NIN + SoC vs SoC was [information protected as a trade secret]. The values are [information protected as a trade secret] the cost-effectiveness threshold referred to in the Reimbursement Act, [information protected as a trade secret]

The biggest limitation of the applicant's economic analysis is the lack of experimental data on the effect of the proposed therapy on the overall survival of patients from the target population and long-term data relating to the efficacy of the proposed technology. [information protected as a trade secret]

However, population size estimates are subject to uncertainty due to the lack of accurate epidemiological data, which constitutes a limitation of the analysis.

In view of the above, financing the proposed technology should be considered reasonable; however, due to the high unit cost and uncertainty of the effect, it seems reasonable to introduce a mechanism securing the payer's budget. This scheme should be based on the reimbursement of the treatment costs in patients for whom treatment has not resulted in a significant inhibition of the decrease in forced vital capacity. [information protected as a trade secret]

## Subject of the application

The order of the Minister of Health concerns the assessment of the appropriateness of public reimbursement of the following medicinal product:

- Ofev (nintedanibum), soft capsules, 150 mg, 60 capsules, EAN code 05909991206468 for which the proposed net sales price is [information protected as a trade secret]
- Ofev (nintedanibum), soft capsules, 100 mg, 60 capsules, EAN code 05909991206444 for which proposed net sales price is [information protected as a trade secret].

Proposed payment and dispensing category: free of charge, the drug is to be applied under the drug programme as part of the already existing limit group - "1173.0 Nintedanib”. [information protected as a trade secret]

## Health problem

Interstitial lung disease is a common disease during systemic sclerosis. In early autopsies, up to 100% of patients showed parenchymal involvement. Up to 90% of patients will show interstitial abnormalities during *high-resolution computed tomography* (HRCT), and 40-75% will show changes during *pulmonary function tests* (PFT). Pulmonary parenchyma involvement usually appears early after *systematic sclerosis* (SSc) diagnosis, and 25% of patients develop clinically significant lung disease within 3 years, defined by physiological, radiological abnormalities or bronchoalveolar lavage (BAL). Risk factors for its development include African-American ethnicity, skin result, serum creatinine and creatine phosphokinase levels, hypothyroidism and cardiac involvement. Genetic factors, specific serological results (anti-topoisomerase and anti-endothelial cells predict the presence of lung involvement, while anti-centromere and antibodies against RNA polymerase III are less associated with lung disease) and type of skin disease (patients with dcSSc have a higher incidence of interstitial disease) all contribute. Predictors of severe restrictive lung disease (defined by forced vital capacity (FVC) ≥50% of the normal value) include African-American ethnicity, male gender, degree of physiological abnormalities at diagnosis (FVC and diffusing capacity for carbon monoxide (DLCO)) and younger age.

In Poland, about 10,000 people suffer from systemic sclerosis, with 4-12 new cases per million inhabitants per year. Systemic sclerosis affects women 3-4 times more often than men. It usually occurs between the age of 30 and 50 but can also start in children or older people.

Interstitial lung disease occurs in approximately 80% in patients with systemic sclerosis. In many of them, the course can be mild or stable and does not require intensive treatment. In 25-30% of patients with interstitial lung disease, especially in the early, aggressive stage of the disease, immunosuppressive therapy is included in case of progression of lung lesions and in the advanced form of the disease.

## Alternative health technology

Taking clinical guidelines, technologies currently funded into consideration [information protected as a trade secret] standard *of care* (SoC) [information protected as a trade secret]. Additional alternative technologies include: cyclophosphamide, azathioprine, lung transplantation and auto-HSCT. However, due to the low use, these comparators were omitted from the analyses.

## Description of the proposed intervention

Nintedanib is a low-molecular-weight inhibitor of tyrosine kinases, including α and β receptors of platelet-derived growth factor (PDGFR), 1-3 (FGFR) and VEGRF 1-3 receptors of fibroblast growth factor. Additionally, nintedanib inhibits lymphocyte-specific protein tyrosine kinase (Lck), protein tyrosine kinase lyn (Lyn), proto-oncogene protein tyrosine kinase src (Src) and colony stimulating factor 1 receptor kinase (CSF1R)

Nintedanib binds competitively with the adenosine triphosphate (ATP) binding site of these kinases and blocks cascades of the transmission of intracellular signals that, as it was shown, play a role in the pathogenesis of tissue fibrosis in interstitial lung disease.

According to the Summary of Product Characteristics (SmPC), Ofev is indicated for use in adults treated with:

- idiopathic pulmonary fibrosis (IPF)
- other progressive chronic interstitial lung diseases (ILD)
- systemic sclerosis-associated interstitial lung disease (SSc-ILD).

The proposed indication is consistent with the registered indication.

Presentations of Ofev containing 60 soft capsules 100 mg (EAN code 05909991206444) and 150 mg (EAN code 05909991206468) under the B.87 drug programme "Treatment of idiopathic pulmonary fibrosis (ICD- 10 J84.1)" are currently reimbursed under catalogue B.

## Efficacy, effectiveness and safety assessment

*This assessment involves collecting data on the health consequences (efficacy and safety) of the new therapy for the health problem in question and of other therapies that are currently reimbursed from public funds and represent alternative therapies available for the health problem. Furthermore, this assessment requires determination of the reliability of data collected and a comparison of the efficacy and safety results of the new therapy against the therapies already available to treat the health problem in question.*

*On the basis of the above, the efficacy and safety assessment allows answering the question of the scale of the health outcome (both in terms of efficacy and safety) to be expected from the new therapy compared with other therapeutic options under consideration.*

The applicant based the clinical and economic analysis mainly on a randomised clinical trial comparing NIN + SoC with PLC + SoC. The trial included 576 patients. The follow-up period was 100 weeks. In addition, the single-arm SENSCIS-ON trial was included, which was an extended phase of the randomised trial. The planned follow-up period is 34 months.

The risk of error in the SENSCIS trial was rated as low according to the Cochrane scale. In contrast, the trial extension (SENSCIS-ON) was rated 6/8 by NICE.

*Efficacy*

Direct comparison of NIN + SoC vs. PLC + SoC - SENSCIS trial

According to the results of the SENSCIS trial, the use of NIN + SoC vs. PLC + SoC was associated with statistically significant improvements in:

- FVC decrease - *medium* difference (MD) was 41.0 ml/year (95% CI: 2.9; 79) - 52.4 ml/year vs. -93.3 ml/year;
- FVC absolute change in respect to initial values – MD=46.4 (95% CI: 8.1; 84.7), -54.6 ml vs -101.0 ml;
- FVC percentage decrease – MD=1.2 (95% CI: 0.1; 2.2), -1.4% vs -2.6%;
- the number of patients with the FVC absolute decrease in respect to initial values of >5% of the normal value - *risk ratio* (RR) was 0.72 (95% CI: 0.54; 0.97), and NNT=13 (95% CI: 7; 110);
- the number of patients with the FVC relative decrease >5% in respect to initial values – RR=0.76 (95% CI: 0.62; 0.94), and NNT=10 (95% CI: 6; 42);
- the number of patients with the FVC absolute decrease in respect to initial values of ≥10% of the normal value or death – RR=0.65 (95% CI: 0.45; 0.93), and NNT=14 (95% CI: 8; 70);
- the number of patients with the FVC absolute decrease in respect to initial values of ≥10% of the normal value or with FVC absolute decrease in respect to baseline values from ≥5% to <10% of the normal value or with the DLCO absolute decrease in respect to initial values of ≥15% of the normal value or death – RR=0.57 (95% CI: 0.40; 0.81), and NNT=10 (95% CI: 6; 25);
- the number of patients with FVC deterioration of 5-10% of the normal value – RR=0.67 (95% CI: 0.47; 0.98), and NNT=16 (95% CI: 8; 221);
- the number of patients with FVC improvement of 5-10% of the normal value – RR=1.94 (95% CI: 1.09; 3.48), and NNT=20 (95% CI: 11; 128);
- the number of patients with a clinically minimal difference in FVC:
    - improvement – RR=1.54 (95% CI: 1.09; 2.18), and NNT=13 (95% CI: 7; 60);
    - improvement or stabilisation – RR=1.18 (95% CI: 1.03; 1.34), and NNT=11 (95% CI: 6; 50);

- deterioration – RR=0.77 (95% CI: 0.63; 0.95), and NNT=11 (95% CI: 6; 50);

There were no statistically significant differences for the comparison of NIN + SoC vs. PLC + SoC in terms of:

- the number of patients with the FVC absolute decrease in respect to initial values of >10% of the normal value;
- the number of patients with the FVC relative decrease of >10% in respect to initial values;
- the number of patients with the FVC absolute decrease in respect to initial values of ≥5% of the normal value or death;
- the number of patients with FVC deterioration by: more than 15%; 10-15%; 0-5%;
- the number of patients with FVC improvement by: more than 15%; 10-15%; 0-5%;
- the number of patients with FVC stabilisation;
- the absolute change in the diffusing capacity for carbon monoxide (DLCO) in respect to initial values;
- absolute and relative change in the modified Rodnan skin scale (mRSS) and absolute change in phalanx ulceration in respect to initial values;
- overall survival for both 52-week and 100-week period.

Quality of life was assessed using questionnaires such as the St George's Respiratory Questionnaire (SGRQ), the Health Assessment Questionnaire-Disability Index (HAQ-DI), the Functional Assessment of Chronic Illness Therapy - Dyspnea (FACIT-Dyspnea), SHAQ, FACIT in the functional domain, EQ-5D-5L and VAS. Significant differences were reported in terms of:

- the St George's Respiratory Questionnaire (SGRQ):
  - limitations in daily activities due to bowel problems - MD=1.39 (95% CI: 0.89; 1.89);
  - limitations in daily activities due to Raynaud syndrome – MD=0.77 (95% CI: 0.28; 1.26);
- Functional Assessment of Chronic Illness Therapy:
  - functional limitations – MD=1.40 (95% CI: 0.30; 2.50);
- EQ-5D-5L (VAS scale):
  - self-assessment of health condition - MD= -3.50 (-6.88; -0.12);
- assessment of health condition by the patient or doctor (VAS scale):
  - global doctor assessment - MD= -0.41 (95% CI: -0.77; -0.05).

<u>Long-term use of NIN (extension of the SENSCIS trial - SENSCIS-ON trial)</u>

The SENSCIS-ON extension trial demonstrated that the average change in FVC in the population that started treatment with NIN is similar to the absolute average change in forced vital capacity in respect to initial values in patients who received NIN for 52 weeks in the randomised phase of the trial (-51.3 ml vs. 54.6 ml). In the PLC group of the SENSCIS trial, the rate of deterioration of the pulmonary function was much higher - the average absolute change in FVC in respect to initial values was -101 ml.

At the same time, it should be noted that the efficacy of NIN treatment in the second year after randomisation appears to be nominally lower than in the first year.

*Safety*

Direct comparison of NIN + SoC vs. PLC + SoC

According to the results of the SENSCIS trial, the use of NIN + SoC vs. PLC + SoC was associated with a statistically significant difference in terms of therapy discontinuation:

- regardless of cause - RR=1.81 (95% CI: 1.20; 2.71), and NNH=11 (95% CI: 6; 34);
- due to adverse events - RR=1.90 (95% CI: 1.15; 3.15) and NNH=15 (95% CI: 8; 62).

There were no statistically significant differences for the comparison of NIN + SoC vs. PLC + SoC regarding therapy discontinuation due to: refusal to continue therapy, failure to adhere to protocol, other reasons.

The proportion of patients requiring dose reduction or temporary discontinuation of therapy was also statistically higher in the intervention group than in the comparator group. Almost half of the patients (139/288) required dose reduction or temporary discontinuation of NIN therapy compared to 12% (35/288) in the PLC group.

The most commonly reported adverse event (AE) was diarrhoea, which developed in 76% of the patients using NIN therapy and in 32% from the PLC group. Diarrhoea was the most common reason for reducing the dose of the drug or discontinuing therapy. Mostly, the course of diarrhoea in the patient was mild (38%) or moderate (34%).

The NIN group also had a statistically significantly higher risk of adverse events such as nausea, vomiting, weight loss and increases in alanine aminotransferase, aspartate aminotransferase or both ≥3xULN. On the contrary, PLC treatment was associated with a higher risk of cough. It was indicated that the NIN group has a 12 times higher risk of a permanent reduction of the dose of the drug and an approximately 8.5 times higher risk of permanent discontinuation of therapy - defined as the consequences of diarrhoea - than in the PLC group.

Long-term use of NIN (extension of the SENSCIS trial - SENSCIS-ON trial)

The profile of the incidence of adverse events associated with the use of nintedanib in the SENSCIS-ON trial is similar to the one reported in the SENSCIS trial. The Allanore 2020b source publication did not examine differences between the group starting treatment in the extended phase and the group continuing treatment with nintedanib.

*Additional safety information*

A document summarising the risk management plan for Ofev was found on the European Medicines Agency (EMA) website. The last update was on 25 January 2021. According to the document, significant adverse reactions (risks) include:

- diarrhoea,
- increased liver enzymes and bilirubin resulting from drug-induced liver injury (DILI),
- bleeding;
- myocardial infarction.

In the event of the occurrence of the above, treatment according to the SmPC for Ofev is recommended. Reducing the dose of the drug, temporarily stopping treatment or discontinuing treatment should be considered when diarrhoea or increased liver enzymes and bilirubin occur. The levels of these parameters should be known before starting treatment and monitored during therapy. Patients with a known risk of bleeding should be treated with nintedanib when the expected benefits outweigh the potential risk. A care should be taken during treatment of patients with a higher risk of cardiovascular disease, while discontinuation of treatment should be considered in patients with acute myocardial ischaemia symptoms. Additionally, according to the EMA document, important potential risks associated with taking Ofev include: venous thromboembolism, arterial thromboembolism excluding myocardial infarction, gastrointestinal perforations, hepatic

insufficiency, teratogenic effects and heart failure.

On the websites of the Food and Drug Administration (FDA) and Medicines and Healthcare products Regulatory Agency (MHRA), the applicant found a communication about the potential risk of aneurysm and artery dissection in patients treated with vascular endothelial growth factor inhibitors, including Ofev. Before starting treatment, it is advisable to carefully consider the risk of aneurysm and artery dissection in patients with risk factors and, if possible, to reduce any risk factors such as hypertension.

*Limitations*

The uncertainty of the presented estimates is affected by the following aspects:

- inhibition of the FVC decrease was presented as the primary endpoint - a functional parameter reflecting the severity of pulmonary fibrosis as a surrogate for overall survival,
- the presented RCT was conducted over a relatively short period of one year,
- In the Highland 2021 publication, the authors highlight the possibility that the treatment with nintedanib in combination with mycophenolate mofetil may have an impact on the comparison results of the NIN group with PLC. No conclusions can be drawn about the effect of mycophenolate on pulmonary function because patients were not randomly chosen for mycophenolate use. There were differences at baseline between subgroups in terms of mycophenolate use, including lower FVC in mycophenolate users than in non-mycophenolate users. Moreover,

  patients taking mycophenolate at the beginning of the trial could only take part in the trial if they had been taking a fixed dose of mycophenolate for at least 6 months before randomisation. Therefore, participants who took mycophenolate at the beginning of the trial did not start taking mycophenolate, but were a population that tolerated mycophenolate and was potentially more likely to respond to mycophenolate,
- no trials on the real efficacy of nintedanib were found.

## Proposed risk-sharing scheme

## [information protected as a trade secret]

## Economic evaluation, including a cost-effectiveness estimation

*Economic evaluation involves estimating and comparing the costs and health outcomes that may be associated with the administration of the new therapy to an individual patient instead of already reimbursed therapies.*

*The costs of therapy are estimated in Polish currency, and health outcomes are usually expressed in life-years gained (LYG) or quality-adjusted life years (QALY) as a result of the therapy.*

*Juxtaposing the values concerning the costs and outcomes of a new therapy and comparing them to the costs and outcomes of already reimbursed therapies allows answering the question of whether the health outcome achieved in an individual patient owing to a new therapy is associated with a higher cost in comparison with already reimbursed therapies.*

*The obtained results of the cost-effectiveness ratio are compared with the so-called cost-effectiveness threshold, i.e. a result that indicates that given the wealth of Poland (expressed in GDP), the maximum cost of the new therapy that is expected to produce a unit of health outcome (1 LYG or 1 QALY) compared to already available therapies should not exceed three times GDP per capita.*

*Currently the cost-effectiveness threshold is PLN 166,758.00 (3 x PLN 55,586.00)*

*The cost-effectiveness ratio does not estimate or determine the value of life, but it only enables its assessment and the use of this assessment to choose the therapy associated with the potential best use of the currently available resources.*

The aim of the analysis was to assess the cost-effectiveness of Ofev (nintedanib) added to standard

therapy compared with alternatives for the treatment of adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD). Cost-utility analysis (CUA) over a lifetime (50-year time) horizon is presented. The NHF and joint perspectives are included. Considering the method according to which the drug is financed (i.e. the drug programme), the patient does not pay for the therapy, so the two perspectives are the same.

The following cost categories were included in the analysis:

- costs of nintedanib;
- costs of SoC;
- costs of diagnostics and therapy monitoring under the drug programme,
- costs of hospitalisation;
- costs of specialist visits;
- costs of other medical procedures;
- costs of adverse event treatment.

[information protected as a trade secret]

*Limitations*

The uncertainty of the presented results is affected by the following aspects:

- the efficacy of the interventions included in the analysis was determined by the results of the SENSCIS trial included in the clinical analysis. The limitations of the clinical analysis affect the limitations of this analysis;
- Overall survival of patients with SSc-ILD was determined by observational studies analysing the effect of a decrease in %FVC by [information protected as a trade secret] on patient survival. The effect of NIN on survival in the analysis is, therefore, predicted indirectly - first, the model determines the %FVC level in a given cycle, and then depending on the occurrence of a decrease in %FVC by at least [information protected as a trade secret], the probability of death is modelled; [information protected as a trade secret]

*Agency's own calculations*

As part of the Agency's own calculations, estimates were made which assumed that within the SoC [information protected as a trade secret] and with these assumptions, NIN threshold prices were calculated relative to individual SoC components.

Assuming that within the SoC [information protected as a trade secret], the NIN threshold price is:

[information protected as a trade secret]

Assuming that, within SoC, [information protected as a trade secret], the NIN threshold price is [information protected as a trade secret]

## Indication whether the circumstances referred to in Art. 13 sec. 3 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs for particular nutritional uses and medical devices (Dz. U. /Journal of Laws/ of 2021, item 523 as amended) do arise.

*If the applicant's clinical analysis does not include randomised clinical trials proving the superiority of the drug over health technologies already reimbursed, the official selling price of the drug must be calculated so that the cost of the drug to be reimbursed is not higher than the cost of the health technology with the most favourable cost–effectiveness ratio.*

The applicant has submitted the randomised trial proving the superiority of NIN+SoC over SoC, so the circumstances described in Art. 13 of the Act on Reimbursement do arise.

## Assessment of the impact on the healthcare system, including the budget impact

*Healthcare system impact assessment has two major parts.*

*First, the analysis of the impact on the payer's budget allows estimating the potential expenses associated with public reimbursement of the new therapy.*

*Estimates of the expenses associated with the new therapy (the "tomorrow" scenario) are compared to how much is currently spent on treating the health problem (the "today" scenario). On this basis, it is possible to assess whether a new therapy will require more resources allocated to the treatment of the given health problem or whether it will result in savings in the payer's budget.*

*The budget impact assessment makes it possible to establish whether the payer has adequate resources to fund a particular technology.*

*Healthcare system impact assessment in the second part answers the question of how the decision on the reimbursement of a new therapy may affect the organisation of the provision of services (particularly in terms of adaptation to the requirements of the implementation of the new therapy) and the availability of other healthcare services.*

The budget impact analysis in case of a positive reimbursement decision for Ofev (nintedanib) added to standard therapy compared to alternative treatments for adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) was conducted over a 2-year time horizon from the public payer perspective and the joint perspective (public payer + patient). Due to the marginal cost on the patient side, the estimate from the joint perspective differs slightly from the patient perspective.

The following cost categories were included in the analysis:

- unit drug costs;
- monitoring under the drug programme and other medical procedures;
- treatment of adverse events.

[information protected as a trade secret]

According to the applicant's estimates, in the event of reimbursing Ofev as proposed in the application, the expenditure from the payer's perspective would increase by:

[information protected as a trade secret]

*Limitations*

The main limitation of the presented results is the lack of precise epidemiological data on the number of patients who could receive the proposed technology. The estimation of the number of patients from the target population was performed on the basis of the compilation of data from various sources (literature data, expert opinions and data from the economic analysis). Combining different data sources with limitations may affect the reliability of the estimates provided.

Moreover, the uncertainty of the presented estimates is affected by the following aspects:

- NHF data indicate a lower number of patients with SSc-ILD than epidemiological data, which may indicate that some cases of SSc-ILD are not correctly diagnosed or reported in Poland. Sensitivity analysis was carried out in this respect;
- [information protected as a trade secret]

**Comments on the proposed risk-sharing scheme**

**[information protected as a trade secret]**

[information protected as a trade secret]

**Comments on the drug programme**

The following inaccuracies were highlighted in verifying the proposed drug programme:

- Point 4 of the proposed drug programme [information protected as a trade secret] indicates: "[information protected as a trade secret]. It does not specify whether this is a [information protected as a trade secret];
- Point 5 of the proposed drug programme [information protected as a trade secret] indicates: [information protected as a trade secret] At the same time, the drug programme does not include the criteria of [information protected as a trade secret] It is worth considering adding to the drug programme explicit criteria for the occurrence of [information protected as a trade secret];

**Discussion on the solutions proposed in the rationalisation analysis**

*The subject of the rationalisation analysis is the identification of a mechanism, the introduction of which will result in the release of public funds in an amount corresponding to at least the increase in costs resulting from a positive decision on the reimbursement of the health technology covered in this recommendation.*

[information protected as a trade secret]

*The rationalisation analysis is submitted if the budget impact analysis for the entity responsible for funding indicates an increase in reimbursement costs.*

In the rationalisation analysis, the applicant proposed a solution that uses the option [information protected as a trade secret]

**Overview of recommendations in relation to the assessed technology**

Seven documents related to the management of pulmonary fibrosis in systemic scleroderma were identified:

- European Dermatology Forum (EDF) 2019 and 2017;
- Polish Diabetes Association (PTD - Polskie Towarzystwo Diabetologiczne) 2017;
- European League Against Rheumatism (EULAR) 2016;
- British Society for Rheumatology (BSR) 2016;
- Fernandez-Codina 2018;
- Hoffman-Vold 2020.

Ofev (nintedanib) was registered for interstitial lung disease in people with systemic sclerosis in Europe in February 2020, and the guidelines found are from 2016-2019 – they do not refer to the use of nintedanib in this patient population.

The clinical guidelines identified cyclophosphamide (with possible further treatment with azathioprine or mycophenolate mofetil), mycophenolate mofetil, hematopoietic stem cell transplantation, rituximab and rituximab with cyclophosphamide as possible therapies in the indication under assessment.

The search did not find any reimbursement recommendations for Ofev in the indication in question. However, information from the All Wales Medicines Strategy Group (AWMSG) regarding the exclusion of the technology from assessment due to an ongoing NICE investigation was identified.

The National Institute for Health and Care Excellence (NICE) 2020 document found by the Agency states that the assessment for the SSc-ILD indication has been suspended due to the assessment for progressive fibrosing interstitial lung disease (PF-ILD), which also covers the indication in question.

[information protected as a trade secret]

## Legal basis for the recommendation

The recommendation was prepared based on the order of the Minister of Health of 6 September 2021 (ref. no.: PLR.4500.421.2021.11.PBO; PLR.4500.420.2021.11.PBO) regarding the preparation of the President's recommendation on the reimbursement of Ofev (nintedanib) under the drug programme: "Nintedanib treatment of systemic sclerosis-associated interstitial lung disease (ICD-10 M34+J99.1)" pursuant to Art. 35 sec. 1 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs intended for particular nutritional uses and medical devices (Dz. U. /Journal of Laws/ of 2021, item 523 as amended), having obtained Position of the Transparency Council No. 126/2021 of 22 November 2021 on the assessment of Ofev (nintedanibum) under the drug programme "Nintedanib treatment of systemic sclerosis-associated interstitial lung disease (ICD-10 M34+J99.1)"

**References**

1. Position of the Transparency Council No. 126/2021 of 22 November 2021 on the assessment of Ofev (nintedanibum) under the drug programme ''Nintedanib treatment of systemic sclerosis-associated interstitial lung disease (ICD-10 M34+J99.1)"
2. Report No. OT.4231.40.2021. Application for the reimbursement of Ofev (nintedanib) under the drug programme: "Nintedanib treatment of systemic sclerosis-associated interstitial lung disease (ICD-10 M34+J99.1)" Verification analysis