

Nintedanib for treating idiopathic pulmonary fibrosis

Technology appraisal guidance

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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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This guidance is partially replaced by TA864.

1 Recommendations

- 1.1 Nintedanib is recommended as an option for treating idiopathic pulmonary fibrosis, only if:
- the person has a forced vital capacity (FVC) between 50% and 80% of predicted
 - the company provides nintedanib with the discount agreed in the patient access scheme and
 - treatment is stopped if disease progresses (a confirmed decline in percent predicted FVC of 10% or more) in any 12-month period.
- 1.2 People whose treatment with nintedanib is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 The technology

- 2.1 Nintedanib (Ofev, Boehringer Ingelheim) targets 3 growth factor receptors involved in pulmonary fibrosis. Nintedanib is thought to block the signalling pathways involved in fibrotic processes, and may reduce disease progression by slowing the decline of lung function. It is administered orally. Nintedanib has a marketing authorisation in the UK 'in adults for the treatment of idiopathic pulmonary fibrosis'.
- 2.2 The summary of product characteristics states that the most frequently reported adverse reactions associated with using nintedanib are diarrhoea, nausea and vomiting, abdominal pain, decreased appetite, decreased weight and increased hepatic enzyme concentrations in the blood. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 2.3 The recommended dosage of nintedanib is 150 mg twice daily. The list price of nintedanib is £2,151.10 for 60 capsules (taken from the company submission and confirmed in Monthly Index of Medical Specialities [MIMS] online, accessed June 2015). This equates to a daily cost of £71.70 (2 capsules per day). The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of nintedanib, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Evidence

The [Appraisal Committee](#) considered evidence submitted by Boehringer Ingelheim and a review of this submission by the [Evidence Review Group](#) (ERG). See the [Committee papers](#) for full details of the evidence.

Clinical effectiveness

- 3.1 The clinical evidence for nintedanib came from 3 multicentre, double-blind, placebo-controlled, randomised trials comprising 2 phase 3 trials (INPULSIS 1 [n=513] and INPULSIS 2 [n=548]) and a phase 2b dose-ranging trial (TOMORROW [n=428]). All 3 trials compared nintedanib with placebo for 52 weeks in adults of 40 years or older with idiopathic pulmonary fibrosis. The primary outcome was the rate of decline (ml per year) in forced vital capacity (FVC). The trials included people with an FVC of at least 50% of the predicted normal value, and a diffusion capacity of the lung for carbon monoxide of 30% to 79% of the predicted normal value at baseline. The mean percent predicted FVC at baseline was approximately 80% in all 3 trials.
- 3.2 The key outcomes from the phase 3 nintedanib trials are presented in tables 1, 2 and 3. The annual rate of decline in FVC with nintedanib (114.7 ml/year) was approximately half that of placebo; this difference was statistically significant ($p<0.001$). Fewer people randomised to nintedanib died compared with placebo, but this difference was not statistically significant. The time to first acute exacerbation was inconsistent across the trials:
- In INPULSIS 1, there was no statistically significant difference between nintedanib and placebo.
 - In INPULSIS 2 the difference showed a benefit in favour of nintedanib, and was statistically significant.
 - The pooled analysis of the 2 trials showed a benefit in favour of nintedanib, which was not statistically significant: 4.9% of people in the nintedanib arm had 1 or more acute exacerbations in 52 weeks compared with 7.6% of people in the placebo arm (HR 0.64, $p=0.08$).

The company noted that the INPULSIS trials were not powered to detect the effect of nintedanib on acute exacerbations.

Table 1 Outcomes from the INPULSIS 1 trial

Study	Annual rate of FVC decline (ml/year)	FVC responders	≥1 acute exacerbation in 52 weeks	Death (all cause)
Nintedanib 150 mg twice daily	-114.7	218 out of 309 (70.6%)	19 out of 309 (6.1%)	13 out of 309 (4.2%)
Placebo	-239.9	116 out of 206 (56.9%)	11 out of 206 (5.4%)	13 out of 206 (6.4%)
Measure of effect HR/MD/OR (95% CI) p value	MD: 125.3 (77.7, 172.8) p<0.001	OR: 1.91 (1.32, 2.79) p<0.001	HR: 1.15 (0.54, 2.42) p=0.67	HR: 0.63 (0.29,1.36) p=0.29

Table 2 Outcomes from the IMPULSIS 2 trial

Study	Annual rate of FVC decline (ml/year)	FVC responders (People with absolute decline in percent predicted FVC <10% at 52 weeks)	≥1 acute exacerbation in 52 weeks	Death (all cause)
Nintedanib 150 mg twice daily	-113.6	229 out of 331 (69.6%)	12 out of 331 (3.6%)	22 out of 331 (6.7%)
Placebo	-207.3	140 out of 220 (63.9%)	21 out of 220 (9.6%)	20 out of 220 (9.1%)
Measure of effect HR/MD/OR (95% CI) p value	MD: 93.7 (44.8, 142.7) p<0.001	OR: 1.29 (0.89, 1.86) p=0.18	HR: 0.38 (0.19, 0.77) p=0.005	HR: 0.74 (0.40, 1.35) p=0.30

Table 3 Outcomes from the pre-planned pooled analysis (IMPULSIS 1 and IMPULSIS 2)
Source of pooled results: nintedanib summary of product characteristics (individual trial results were presented in the company submission)

Study	Annual rate of FVC decline (ml/year)	FVC responders (People with absolute decline in percent predicted FVC <10% at 52 weeks)	≥1 acute exacerbation in 52 weeks	Death (all cause)
Nintedanib 150 mg twice daily	-113.6	447 out of 638 (70.1%)	31 out of 638 (4.9%)	35 out of 638 (5.5%)
Placebo	-223.5	256 out of 423 (60.5%)	32 out of 423 (7.6%)	33 out of 423 (7.8%)
Measure of effect HR/MD/ OR (95% CI) p value	MD: 109.9 (75.9, 144.0) p<0.0001	OR: 1.58 (1.21, 2.05) p=0.0007	HR: 0.64 (0.39, 1.05) p=0.08	HR: 0.70 (0.43, 1.12) p=0.14

Abbreviations: CI, confidence interval; FVC, forced vital capacity; HR, hazard ratio; MD, mean difference; OR, odds ratio.

- 3.3 Subgroup analyses showed that there were no statistically significant differences between the effectiveness of nintedanib on slowing lung function decline in people with a percent predicted FVC of 50% to 80% and people with a percent predicted FVC of more than 80%.
- 3.4 To compare nintedanib with pirfenidone, the company did a network meta-analysis including the 3 nintedanib trials and 5 placebo-controlled trials of pirfenidone (SP2, SP3, CAPACITY 1, CAPACITY 2 and ASCEND) which informed its economic model. The company chose different trials for different end points in the model:
- It included evidence from all the trials for overall survival.
 - It excluded the 2 pirfenidone trials in Japanese populations (SP2 and SP3) for acute exacerbations, because of heterogeneity (differences compared with other studies, including longer disease duration and a different proportion of people who smoke).
 - It excluded the ASCEND study of pirfenidone for decline in lung function.

The results are presented in table 4. The base-case results for overall survival were the same for nintedanib and pirfenidone, and neither drug showed a statistically significant difference in mortality compared with placebo. The base-case analysis of acute exacerbations showed comparable benefits for nintedanib and pirfenidone compared with placebo, but the company reported uncertainty in the results, which it considered to be a result of heterogeneity in the Japanese trials of pirfenidone (SP2 and SP3). After excluding these trials from the network meta-analysis ('scenario 3' of the sensitivity analyses for this outcome), the results showed fewer acute exacerbations with nintedanib than pirfenidone. The company's analysis of loss of lung function (defined by the company as an absolute decline in percent predicted FVC of at least 10%) gave similar results for nintedanib and pirfenidone using the base-case network meta-analysis. The differences in loss of lung function between each drug and placebo were statistically significant. After excluding the ASCEND trial of pirfenidone from the network meta-analysis because of heterogeneity ('scenario 2' of the sensitivity analyses for this outcome), the results suggested that nintedanib was more effective than pirfenidone at reducing loss of lung function, however the company did not state whether this difference was statistically significant.

- 3.5 The company evaluated 4 safety outcomes in its network meta-analysis. It reported that, compared with people receiving placebo, those receiving nintedanib were more likely to have severe gastrointestinal events ($p=0.055$), stop the study drug ($p=0.014$), and have adverse events that led to stopping the study drug ($p=0.007$). These differences were statistically significant. Nintedanib was associated with fewer serious cardiac events than placebo and pirfenidone, but the odds ratios were not statistically significant. Nintedanib was associated with more serious gastrointestinal events than pirfenidone (odds ratio 3.96, 95% confidence interval [CI] 1.18 to 14.51, p value not reported). The company reported that, compared with pirfenidone, nintedanib was associated with lower rates of stopping because of adverse events (odds ratio 0.88, 95% CI 0.57 to 1.37, difference not statistically significant).

Table 4 Network meta-analysis of efficacy: scenarios used in the company cost-effectiveness model

Comparison	Overall survival: Median odds ratio (95% CI), fixed effect model (NMA base case: all evidence)	Acute exacerbations: Median odds ratio (95% CI), fixed effect model (NMA scenario 3: excluded heterogeneous trials)	Loss of lung function(defined as an absolute decline in percent predicted FVC of over 10% by the end of the study follow-up): Median odds ratio (95% CI), fixed effect model (NMA scenario 2: excluded heterogeneous trial)
Nintedanib compared with placebo	0.70 (0.45, 1.10)	0.56 (0.35, 0.89) statistically significant	0.54 (0.42, 0.69) statistically significant
Pirfenidone compared with placebo	0.70 (0.46, 1.05)	1.01 (0.22, 4.50)	0.69 (0.47, 1.00) statistically significant
Nintedanib compared with pirfenidone (results of significance testing not reported)	1.00 (0.55, 1.85)	0.56 (0.12, 2.68)	0.78 (0.49, 1.22)

Abbreviations: CI, confidence interval; FVC, forced vital capacity; NMA, network meta-analysis.

ERG comments

- 3.6 The ERG highlighted that the 3 nintedanib trials enrolled people with a percent predicted FVC of at least 50% and therefore did not provide evidence for people with more severe disease.
- 3.7 The ERG was concerned that the company did not fully explain how lung function, physical function or acute exacerbations predict the course and outcome of the disease in patients. Therefore it was unclear which specific outcomes were the most clinically meaningful.
- 3.8 The ERG's key concern with the network meta-analysis was the potential for bias in favour of nintedanib because the company excluded studies in some scenarios.

Cost effectiveness

3.9 The company provided a Markov model to assess the cost effectiveness of nintedanib compared with pirfenidone or best supportive care in adults with idiopathic pulmonary fibrosis. The company modelled people with a percent predicted FVC of 50% or more (although the marketing authorisation does not have a restriction related to FVC). The model used a lifetime time horizon, with a cycle length of 3 months.

3.10 The 19 health states in the model used a combination of 2 measures: percent predicted FVC (defined as approximately 10 percentage point increments) and the occurrence of an acute exacerbation. People entered the model in different health states based on percent predicted FVC and without having had an exacerbation. They could remain in the same health state or move through the model to different health states by:

- loss of lung function (representing disease progression, defined as a 10 percentage point decrease in percent predicted FVC)
- exacerbation
- loss of lung function and exacerbation
- death.

Once a person progressed to a health state with a lower percent predicted FVC it was not possible to return to a health state with better lung function. Once an exacerbation occurred, a person could not move back to a health state without exacerbation. Exacerbation health states had different health outcomes and costs from health states without exacerbation. If a person had a second exacerbation they did not move into a different health state. Instead they incurred a short-term cost and disutility associated with an exacerbation. Because there was no evidence on the incidence of recurrent exacerbations, the company assumed that a person who had at least 1 exacerbation had the same risk of another exacerbation as a person who had never had an exacerbation. Death could occur at any point in the model, or when a person's percent predicted FVC reduced to 39.9% or less.

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- 3.11 The company modelled the baseline risks of mortality, disease progression (loss of lung function), and acute exacerbations using the results from the placebo arm of the nintedanib clinical trials (INPULSIS and TOMORROW). It based the efficacy of best supportive care on the results from the placebo arms of the INPULSIS trials. The company applied odds ratios from its network meta-analysis to the baseline risks to estimate the relative effectiveness and safety of nintedanib and pirfenidone compared with best supportive care. To extrapolate data beyond what were available from clinical trials, the company fitted the following parametric models:
- a log logistic model to estimate overall survival
 - an exponential model to estimate the probability of exacerbation and stopping medication
 - a logistic regression model to predict loss of lung function.
- 3.12 The company included adverse events in the model if they: substantially affected costs and quality-adjusted life years (QALYs), had an incidence of more than 5%, or an incidence 1.5 times greater than in the comparator arm. The company excluded the adverse event diarrhoea, even though it occurred commonly in the INPULSIS trials (reported in over 60% of people receiving nintedanib compared with 19% of people receiving placebo), because the condition was usually mild to moderate in severity and resulted in less than 5% of people stopping treatment.
- 3.13 The company included the following costs in its model: drug treatments (including concomitant medications), adverse events, liver function tests, resource use (for drug acquisition, patient monitoring, treating acute exacerbations and adverse events), oxygen use, exacerbations, and end-of-life care. The company assigned utility values to each health state in the model using EQ-5D data collected in the INPULSIS trials. The model also incorporated disutilities from exacerbations and treatment-related adverse events.
- 3.14 Both nintedanib and pirfenidone had a confidential patient access scheme (price discount) agreed with the Department of Health. At the request of NICE, the company (Boehringer Ingelheim) provided its base-case results and sensitivity analyses using the list prices of nintedanib and pirfenidone. NICE requested that the ERG provide the results of its own exploratory analyses including the list

prices, and, separately in a confidential appendix, with both discounts incorporated.

3.15 In the company's deterministic base case, best supportive care was associated with 3.27 QALYs; pirfenidone with 3.62 QALYs and nintedanib with 3.67 QALYs. Using the list prices for nintedanib and pirfenidone, nintedanib dominated pirfenidone (that is, nintedanib was more effective and was cost saving) and produced an incremental cost-effectiveness ratio (ICER) of £149,361 per QALY gained compared with best supportive care. The company did sensitivity and scenario analyses around its base case (using list prices for nintedanib and pirfenidone). The comparison between nintedanib and pirfenidone was sensitive to using the stopping rule (when people stop treatment if their percent predicted FVC declines by 10% or more in 1 year):

- When the stopping rule was applied only to people receiving pirfenidone, the ICER for nintedanib was £82,784 per QALY gained compared with pirfenidone.
- When the stopping rule was applied to both the nintedanib and pirfenidone arms, the ICER for nintedanib was £17,096 per QALY gained compared with pirfenidone.

The comparison between nintedanib and best supportive care was very sensitive to estimates of mortality risk associated with treatment. Changing the baseline survival risk (by using an alternative method of extrapolation) increased the ICER by approximately:

- £91,000 per QALY gained when the company used a Weibull parametric model
- £320,000 per QALY gained when it used a Gompertz parametric model.

3.16 When the ERG applied the patient access schemes for nintedanib and pirfenidone to the company base case, pirfenidone was extendedly dominated by nintedanib and best supportive care (meaning that a combination of best supportive care and nintedanib would give more benefit than pirfenidone and would be cost saving). The ICER for nintedanib compared with best supportive care was substantially over £30,000 per QALY gained. In a pairwise comparison, the ICER for nintedanib compared with pirfenidone was between £20,000 and £30,000 per

QALY gained. NICE cannot report the exact ICERs because the patient access schemes are confidential.

ERG comments and additional analyses

- 3.17 The ERG's clinical adviser considered that people who have had 1 exacerbation were at higher risk of recurrent exacerbation than those who have not had any.
- 3.18 The ERG suggested that the population in the company's model may not represent those treated in clinical practice in England because it included people with percent predicted FVC of more than 80% (accounting for approximately 45% of people in the model). The ERG noted that clinical advice during the pirfenidone appraisal (see NICE's previous technology appraisal guidance TA282 on pirfenidone for treating idiopathic pulmonary fibrosis, now replaced by [TA504 pirfenidone for treating idiopathic pulmonary fibrosis](#)) suggested that this FVC represents disease that is milder than would typically be treated in current practice.
- 3.19 The ERG suggested that the results of the company's cost-effectiveness analysis may have been biased, because the company chose a different scenario analysis from its network meta-analysis to inform the relative effectiveness of nintedanib and pirfenidone for each different outcome.
- 3.20 The ERG suggested that the company model overestimated disutilities for adverse events, and suggested alternative estimates, because:
- Adverse events in the company's model last for 1 year; the ERG considered that for gastrointestinal and skin disorders the duration would be shorter than this and suggested a duration of 1 month based on published data.
 - Data from a long-term open-label extension study of the CAPACITY trials of pirfenidone (the RECAP study) suggested that the incidence of rash was lower than the estimates in the company model.
 - The company may have overestimated the incidence of photosensitivity associated with pirfenidone, which the ERG suggested patients can prevent by avoiding sun exposure.

The ERG also noted the disutility associated with new exacerbations that the company included in its submission (–0.14) did not match the disutility the company used in its model (0.0987).

Additional analyses

- 3.21 After consultation, the company increased the simple discount to the price of nintedanib. The company updated its analysis with the lower price and also included different results from the network meta-analysis in line with the Committee's preferred assumptions (see [section 4.6](#)). The company included all the trial evidence in the network meta-analysis for the outcomes of lung function, serious cardiac events, gastrointestinal events and probability of stopping the drug. The SP2 trial comparing pirfenidone with placebo in a Japanese population, which provided evidence in the network meta-analysis for overall survival and acute exacerbations, was considered to be an outlier by the Committee. Therefore the company excluded the SP2 study from the network meta-analysis for these outcomes. The company included a risk of death of 2.79% over 6 months for people with an exacerbation (previously the company did not model a link between exacerbation and life expectancy). It also reduced the duration of adverse events from 1 year to 1 month and corrected the disutility associated with new exacerbations (see [section 4.11](#) for the Committee's preferred assumptions on disutilities). The company did not reduce the incidence of photosensitivity, but the ERG advised that this no longer affected the ICERs because the company had reduced the duration of adverse events to 1 month. As in the company's base case, the company modelled a population with percent predicted FVC of more than 50% but did not include the stopping rule. Using the list prices for nintedanib and pirfenidone, nintedanib dominated pirfenidone and was associated with an ICER of £145,310 per QALY gained compared with best supportive care. The ICER for pirfenidone compared with best supportive care was £172,208 per QALY gained.
- 3.22 After consultation, when the ERG applied the patient access schemes for nintedanib and pirfenidone to the company's revised analysis, nintedanib dominated pirfenidone. The ICER for nintedanib compared with best supportive care remained substantially over £30,000 per QALY gained. The ICER for

pirfenidone compared with best supportive care was also substantially over £30,000 per QALY gained. The results were similar when restricting the population to people with percent predicted FVC of 50% to 79.9% or 80% or more. However, the ERG highlighted that it would expect differences in treatment costs, efficacy and other model parameters for different subgroups defined by percent predicted FVC, and that these differences would likely influence cost effectiveness. Therefore, the results for subgroups should be interpreted with caution.

- 3.23 The ERG presented results with the stopping rule applied (that is, treatment is stopped if percent predicted FVC declines by more than 10%) for both nintedanib and pirfenidone and, separately, for pirfenidone only. The patient access schemes were included for both drugs. For the population with percent predicted FVC of more than 50% and also for the subset of the population with percent predicted FVC of 50% to 79.9%, applying the stopping rule for both treatments resulted in nintedanib dominating pirfenidone. When the ERG applied the stopping rule for pirfenidone only, the ICER for nintedanib compared with pirfenidone was between £20,000 and £30,000 per QALY gained in both populations. The ERG did not report the ICERs with the stopping rule for the population with percent predicted FVC of 80% or more. The ICER for pirfenidone compared with best supportive care remained substantially over £30,000 per QALY gained when the stopping rule was applied. NICE cannot report the exact ICERs because the patient access schemes are confidential.

4 Committee discussion

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of nintedanib, having considered evidence on the nature of idiopathic pulmonary fibrosis and the value placed on the benefits of nintedanib by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical management

- 4.1 The Committee understood that idiopathic pulmonary fibrosis is a distressing illness that limits physical activity because of breathlessness, and can lead to hypoxia, pulmonary hypertension, heart failure and death. The Committee heard from clinical experts that 80% of people with idiopathic pulmonary fibrosis die from the condition or from respiratory failure. The median overall survival in the clinical trials, which excluded people with the most severe disease, was 3 to 4 years. It heard that there is no cure for idiopathic pulmonary fibrosis, although the Committee acknowledged that pirfenidone and lung transplant (when drug treatment is not appropriate) are options available to manage the condition. It heard however that these are not appropriate for many people because of the tolerability of pirfenidone, the severity of the person's condition, or other comorbidities. Patient experts explained that a key aim of treatment is to slow the progression of disease. They stated that people with idiopathic pulmonary fibrosis would benefit from alternative treatment options. The Committee concluded that idiopathic pulmonary fibrosis is associated with substantial morbidity and mortality, and that there are few treatment options.
- 4.2 The Committee discussed the effect of acute exacerbations in idiopathic pulmonary fibrosis, which it understood to be more serious than exacerbations in other respiratory diseases. It heard from clinical experts that half of people with idiopathic pulmonary fibrosis will die within 30 days of an acute exacerbation. People who survive an exacerbation have permanent and substantially reduced lung function (up to a 20% decline in percent predicted forced vital capacity [FVC]). Clinical experts explained that acute exacerbations can be difficult to define in clinical trials, because they can be confused with respiratory infections,

but are clearly recognised in clinical practice by experienced clinicians. The Committee heard from patient experts that preventing or delaying acute exacerbations is an important way to maintain quality of life. The Committee concluded that exacerbations are an important clinical event, but can be difficult to define, particularly in clinical trials.

4.3 The Committee considered how clinicians assess lung function in people with idiopathic pulmonary fibrosis. It understood that clinicians use a number of measures of lung function, and heard that they routinely use percent predicted FVC to guide clinical decision-making. Clinical experts noted some disadvantages with using percent predicted FVC. For example, the equations used to calculate percent predicted FVC (adjusting for age, sex and height) extrapolate data from a middle-aged white male population and may under- or overestimate the expected lung volume for current clinical practice in England. Clinical experts explained that it is difficult to know how a person's lung function would have progressed without treatment. However, the Committee acknowledged that this is not unique to idiopathic pulmonary fibrosis. The Committee heard from clinical experts that other measures of lung function (such as the 6-minute walk test distance and diffusion capacity of the lung for carbon monoxide) are less reliable than FVC. The company stated that emphysema commonly co-exists with idiopathic pulmonary fibrosis, and that in people with both conditions, percent predicted FVC can be less sensitive (that is, it could be high despite significant pulmonary disease) and can change from one day to the next. The Committee recognised the limitations of FVC but understood that in clinical practice the wider patient characteristics would be taken into account in interpreting percent predicted FVC. Clinical experts noted that they follow the stopping rule in NICE's previous technology appraisal guidance TA282 on pirfenidone for treating idiopathic pulmonary fibrosis, now replaced by [TA504 pirfenidone for treating idiopathic pulmonary fibrosis](#), but explained that before withdrawing treatment they retest FVC to confirm that the 10% drop is not temporary, which might happen with an infection. The Committee concluded that, although it has some limitations, percent predicted FVC is the most reliable and widely used measure of lung function in clinical practice.

4.4 The Committee discussed the treatment options for people with idiopathic pulmonary fibrosis.

- It heard that pirfenidone is normally offered to people whose disease meets

the criteria in the NICE guidance for pirfenidone: that is, people with a percent predicted FVC of 50% to 80%. It heard that this group represents around half of the population with idiopathic pulmonary fibrosis in the UK, but that around 30% of people could not tolerate pirfenidone.

- The Committee heard that people with a percent predicted FVC of more than 80% represent around one third of people with idiopathic pulmonary fibrosis. It heard from clinical experts that this group would be offered best supportive care because pirfenidone is not recommended in this population.
- Clinical experts explained that drug treatment might not be appropriate for people with a percent predicted FVC of less than 50% (more severe disease). The aim of treatment in this population is to maintain quality of life, and lung transplant might be explored as an option.

The Committee concluded that in clinical practice nintedanib would be appropriate for treating people with a percent predicted FVC of more than 50%.

Clinical effectiveness

- 4.5 The Committee discussed the clinical trial evidence for nintedanib and heard that the trials reflected current clinical practice. It understood that there were inconsistencies in some of the results across the 2 phase 3 trials. However, it noted that a pre-planned pooled analysis showed statistically significant differences between nintedanib and placebo for loss of lung function and a non-significant benefit in favour of nintedanib for reducing acute exacerbations. The Committee heard that, based on pre-planned and post-hoc subgroup analyses, nintedanib was effective regardless of the baseline FVC. It noted that the mean baseline percent predicted FVC was approximately 80% across all 3 nintedanib trials, indicating that the trials provided evidence for treating idiopathic pulmonary fibrosis in people with a percent predicted FVC above 80%. The Committee concluded that the trials provided an appropriate basis for its decision-making, and showed that nintedanib is more effective than placebo in all subgroups.

- 4.6 The Committee considered whether the company network meta-analysis was robust. It heard from the ERG that the company had included all relevant trials, but had explored heterogeneity in the results by excluding trials in sensitivity analyses. The Committee understood that the results of the network meta-analysis informed the relative effectiveness of nintedanib and pirfenidone in the company model. It heard that the company used the results of different sensitivity analyses (that is, using data from different sets of trials) for different outcomes in the model (see [section 3.4](#)). The Committee agreed that this introduced a potential bias in favour of nintedanib because the results of the analyses chosen by the company were more favourable to nintedanib than the results from analyses including all trials. It concluded that the same trials should be included for all outcomes. The Committee agreed with excluding one of the Japanese studies (SP2) because it considered it to be an outlier. The company clarified that not all trials reported evidence for all outcomes considered in the model, and presented an updated analysis excluding the SP2 study from the relevant outcomes (overall survival and acute exacerbations). The Committee concluded that the updated network meta-analysis provided a more appropriate basis for its decision-making. The Committee considered the effectiveness of nintedanib and discussed the results of the company network meta-analysis and concluded that the clinical effectiveness of nintedanib is similar to pirfenidone.

Cost effectiveness

- 4.7 The Committee considered whether the company model, in which health states were based on percent predicted FVC and occurrence of acute exacerbations, accurately represents the progression of idiopathic pulmonary fibrosis. It heard from patient experts that idiopathic pulmonary fibrosis is a progressive disease which does not improve, and noted that the model reflects this. The Committee heard from the company that exacerbations increased the rate of disease progression (that is, loss of lung function) in the model, which the Committee considered appropriate. However, taking into account the clinical experts' comments about the substantial impact of exacerbations on quality of life (see [section 4.2](#)), the Committee was concerned that the results of the model were not sensitive to changes in the rate of exacerbations. The ERG stated that it considered the methods applied in the company's economic analyses to be generally appropriate. The Committee concluded that a model based on percent

predicted FVC and exacerbations was appropriate for decision-making.

- 4.8 The Committee discussed the population included in the economic model. The Committee appreciated that its remit was to compare nintedanib with current NHS treatment which, for people with percent predicted FVC of 50% to 80%, is pirfenidone or best supportive care. For people with percent predicted FVC of more than 80%, current NHS treatment is best supportive care. It noted that the company analyses included a population with a percent predicted FVC of more than 50%, and that the ERG modelled a restricted population with a percent predicted FVC of 50% to 79.9%. The Committee recognised that the ERG had assumed that people with a percent predicted FVC of 80% or more do not present in clinical practice. However, the Committee heard from the clinical experts that people with a percent predicted FVC of 80% or more represent a third of people with idiopathic pulmonary fibrosis in specialist clinical practice (see section 4.4), and that the relevant comparator for this population is best supportive care. The Committee agreed that to compare nintedanib with best supportive care, it would have preferred to see a model representing only people with a percent predicted FVC of 80% or more. After consultation, the ERG provided an analysis in people with a percent predicted FVC of 80% or more. The Committee noted the ERG's concerns that subgroup analyses were subject to limitations because parameters such as hazard ratios, mortality rates, and rates of stopping treatment may differ between the subgroups and the whole population. In the absence of subgroup-specific parameters, the Committee concluded that the company model was appropriate for its decision-making.
- 4.9 The Committee considered the extrapolations of overall survival based on the company model. It noted that the company and the ERG had used the log logistic curve in their base-case analyses. The Committee discussed whether this curve was appropriate given that it has a long tail, meaning that the model might overestimate life expectancy and therefore underestimate the incremental cost-effectiveness ratio (ICER) for nintedanib. The Committee noted that using other methods to extrapolate survival substantially increased the ICER for nintedanib compared with best supportive care. The Committee heard from the clinical experts that the median survival estimated with the log logistic curve generally reflects the natural history of treated disease. The Committee agreed that the survival modelling was uncertain, but noted that it had little effect on the ICER when comparing nintedanib with pirfenidone because the company had

assumed equal survival with these drugs. Any differences in quality-adjusted life year (QALY) gain between nintedanib and pirfenidone were therefore derived from differences in quality of life. The Committee concluded that the log logistic curve was sufficient for decision-making, but recognised that the ICER for nintedanib compared with best supportive care, when using the log logistic curve, may be an underestimate.

- 4.10 The Committee discussed the utility values in the company's model. It approved of the company using trial-based EQ-5D data to estimate health-state utility values. The Committee expressed some concern that the company did not include a disutility for diarrhoea in the model, because this is a common adverse event with nintedanib that it considered would worsen quality of life. It heard from the company that including a diarrhoea-related disutility would not affect the model results because the event was mild-to-moderate and led to less than 5% of people stopping treatment in the nintedanib clinical trials. However, the Committee did not agree that diarrhoea would have no clinical impact.
- 4.11 The Committee considered the changes to adverse-event-related disutilities suggested by the ERG. It heard from clinical experts that the ERG's preferred estimate of rash-related disutility (based on data from the RECAP study) was inaccurate because the RECAP study underestimated the incidence of rash by 50%. Clinical experts agreed with the ERG's choice of a lower incidence of photosensitivity with pirfenidone, and stated that it was reasonable to assume people have adverse events in the model for approximately 1 month rather than for 1 year (as in the company base case). The Committee concluded that the estimate of rash-related disutility in the company's original base case was more appropriate than the ERG's estimate, but that the ERG provided more accurate estimates of other disutilities which the company incorporated in its revised base case (see [sections 3.21 and 3.22](#)).
- 4.12 The Committee compared the company model with the model submitted for NICE's previous technology appraisal guidance TA282 on pirfenidone for treating idiopathic pulmonary fibrosis, now replaced by [TA504 pirfenidone for treating idiopathic pulmonary fibrosis](#), for external validation. It noted that the nintedanib model produced different results from the pirfenidone model, when comparing pirfenidone with best supportive care. The ERG could not fully compare the 2 models because of confidentiality, but explained some key differences. For

example, treatment effect in the pirfenidone model was based on FVC and the 6-minute walk test distance. However, the Committee understood from clinicians that the 6-minute walk test distance was an unreliable measure. The pirfenidone model did not include acute exacerbations, which the Committee understood to be an important clinical event in idiopathic pulmonary fibrosis. The pirfenidone model used a mapping algorithm to calculate utility values, whereas the nintedanib model included trial-based EQ-5D data. The Committee concluded that it could not compare the models fully, but that the current model for nintedanib was robust, and appropriate for decision-making.

4.13 The Committee considered whether it should take into account the consequences of the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism, when appraising nintedanib. The Appraisal Committee noted NICE's position statement in this regard, and accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The Committee heard nothing to suggest that there is any basis for taking a different view with regard to the relevance of the PPRS to this appraisal of nintedanib. It therefore concluded that the PPRS payment mechanism was not applicable for considering the cost effectiveness of nintedanib.

4.14 The Committee discussed the most plausible ICER. It noted that the most plausible scenario would include its preferred assumptions for:

- disutilities for adverse events (see section 4.11)
- estimates of overall survival, acute exacerbations, loss of lung function, adverse events, and stopping treatment odds ratios for nintedanib compared with pirfenidone (see section 4.6).

The Committee considered the population for which pirfenidone and best supportive care were comparators (that is, people with a percent predicted FVC of 50% to 80%). The Committee was aware that the company presented a revised base case incorporating the Committee's preferred assumptions but without stopping rules for nintedanib or pirfenidone. The Committee understood that NICE guidance for pirfenidone recommends that pirfenidone treatment should be stopped if there is evidence of disease progression (a

decline in percent predicted FVC of 10% or more in any 12-month period). The Committee noted comments from consultation that there was no clinical basis for applying a stopping rule for nintedanib. However, the Committee appreciated that stopping rules generally improve cost effectiveness by minimising continued treatment in people for whom a drug is not effective, and understood that the 10% value was determined during the pirfenidone appraisal. The Committee heard that when the ERG included this stopping rule and the patient access schemes for both nintedanib and pirfenidone in the company's revised base case, nintedanib dominated pirfenidone (meaning that nintedanib was cost saving and more effective than pirfenidone). Applying this stopping rule for pirfenidone but not nintedanib resulted in an ICER of between £20,000 and £30,000 for nintedanib compared with pirfenidone. The Committee noted that the exact ICER was towards the upper end of the £20,000 to £30,000 range. The Committee was mindful of its consideration that the clinical effectiveness of nintedanib is similar to pirfenidone (see section 4.6) and was aware that not including a stopping rule for nintedanib would make it more costly than pirfenidone for similar benefits. The Committee was also mindful that compared with best supportive care, the ICERs for both nintedanib (see section 4.15) and pirfenidone (see [sections 3.21 and 3.22](#)) were substantially higher than the range considered a cost-effective use of NHS resources. For these reasons, the Committee agreed that nintedanib could not be considered cost effective without a stopping rule. The Committee concluded that nintedanib could be considered cost effective compared with pirfenidone in people with a percent predicted FVC of 50% to 80% when the stopping rule for nintedanib was applied.

- 4.15 The Committee considered the population with a percent predicted FVC of more than 80%, for whom the comparator is best supportive care. The Committee would have preferred to see a model only of people with a percent predicted FVC of more than 80%, but in the absence of appropriate subgroup-specific parameters (see section 4.8) the Committee considered that the company model of people with a percent predicted FVC of more than 50% was appropriate for decision-making. It noted that the ICER for nintedanib compared with best supportive care was substantially greater than £30,000 per QALY gained. The Committee acknowledged that the ICER based on the ERG's exploratory analysis including only people with a percent predicted FVC of 80% or more was also

substantially greater than £30,000 per QALY gained. NICE cannot report the ICERs because the patient access schemes are confidential. The Committee noted comments that nintedanib is clinically effective in all subgroups and that it is not clinically beneficial to delay treatment until the condition worsens. However, the Committee was aware of the high ICERs estimated for nintedanib compared with best supportive care. The Committee concluded that the ICERs for nintedanib compared with best supportive care in people with a percent predicted FVC of more than 80% were not within the range considered to be a cost-effective use of NHS resources.

- 4.16 The Committee heard from patient experts and Committee members that nintedanib was innovative in its potential to make a significant and substantial impact on health-related benefits. The patient expert emphasised the better tolerability profile associated with nintedanib which significantly improved their quality of life. For example, the patient expert valued their opportunity to pursue outdoor activities while receiving nintedanib, which they had been unable to do when receiving pirfenidone because of the associated photosensitivity. The Committee acknowledged that nintedanib is associated with adverse events that are not commonly associated with pirfenidone, such as serious gastrointestinal events, and that diarrhoea is more common with nintedanib than pirfenidone, but heard from clinical and patient experts that people may tolerate nintedanib better than pirfenidone. The Committee also noted that people do not need to take nintedanib as often as pirfenidone but heard differing views about the value of this, and considered this a small advantage. On balance, the Committee concluded that there are benefits associated with nintedanib that the economic model does not fully capture, such as the impact on patients' lives of nintedanib's better tolerability profile and reduced dosing frequency, compared with pirfenidone. The Committee concluded that there may be some additional gains in health-related quality of life over those already included in the QALY calculations, supporting its recommendation that nintedanib should be offered to people as an alternative to pirfenidone.

5 Implementation

- 5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.
- 5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.
- 5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has idiopathic pulmonary fibrosis and the healthcare professional responsible for their care thinks that nintedanib is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Appraisal Committee members and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes of each Appraisal Committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Amanda Adler (Chair)

Consultant Physician, Addenbrooke's Hospital, Cambridge

Professor Ken Stein (Vice Chair)

Professor of Public Health, University of Exeter Medical School

Dr Ray Armstrong

Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson

Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Professor John Cairns

Professor of Health Economics Public Health and Policy, London School of Hygiene and

Tropical Medicine

Mr Matthew Campbell-Hill

Lay member

Mr David Chandler

Lay member

Mr Mark Chapman

Health Economics and Market Access Manager, Medtronic UK

Professor Imran Chaudhry

Lead Consultant Psychiatrist and Deputy Associate Medical Director, Lancashire Care NHS Foundation Trust

Professor Daniel Hochhauser

Consultant in Medical Oncology, UCL Cancer Institute

Dr Neil Iosson

Locum General Practitioner

Mrs Anne Joshua

NHS 111 Pharmacy Lead, Patients and Information, NHS England

Dr Sanjay Kinra

Reader in Clinical Epidemiology and Honorary Consultant in Paediatrics, London School of Hygiene and Tropical Medicine and University College London NHS Hospitals Trust

Dr Miriam McCarthy

Consultant, Public Health, Public Health Agency, Northern Ireland

Mr Christopher O'Regan

Head of Health Technology Assessment and Outcomes Research, Merck Sharp & Dohme

Dr John Pounsford

Consultant Physician, Frenchay Hospital, Bristol

Dr Danielle Preedy

Lay member

Ms Marta Soares

Research Fellow, Centre for Health Economics, University of York

Dr Nicky Welton

Senior Lecturer in Biostatistics and Health Technology Assessment, University of Bristol

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal) and a project manager.

Sophie Laurenson

Technical Lead

Jeremy Powell

Project Manager

7 Sources of evidence considered by the Committee

The Evidence Review Group (ERG) report for this appraisal was prepared by Southampton Health Technology Assessments Centre (SHTAC):

- Cooper K, Kalita N, Rose M, et al. Nintedanib for treating idiopathic pulmonary fibrosis: A Single Technology Appraisal, July 2015

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Companies were also invited to make written submissions. Professional or expert and patient or carer groups, and other consultees, had the opportunity to make written submissions. Companies, professional or expert and patient or carer groups, and other consultees, also have the opportunity to appeal against the final appraisal determination.

Company:

- Boehringer Ingelheim

Professional or expert and patient or carer groups:

- Action for Pulmonary Fibrosis
- British Thoracic Society
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- United Kingdom Clinical Pharmacy Association

Other consultees:

- Department of Health

- NHS England
- NHS Nottingham City CCG
- Welsh Government

Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Roche Products

The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on nintedanib by attending the initial Committee discussion and providing a written statement to the Committee. They were also invited to comment on the ACD.

- Dr Toby Maher, Consultant Respiratory Physician, nominated by NHS England – clinical expert
- Phillip Lloyd Mayers, Specialist Respiratory and ILD Pharmacist, nominated by United Kingdom Clinical Pharmacy Association – clinical expert
- Michael Bray, Chair of trustees for Action for Pulmonary Fibrosis, nominated by Action for Pulmonary Fibrosis – patient expert
- Peter Burns, Secretary of Papworth IPF patient support group, nominated by Pulmonary Fibrosis Trust – patient expert

Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy. They were also invited to comment on the ACD.

- Boehringer Ingelheim

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