Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2513

nintedanib soft capsules (Ofev®)

Boehringer Ingelheim

10 February 2023

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a resubmission assessed under the orphan equivalent medicine process

nintedanib (Ofev®) is accepted for restricted use within NHSScotland.

Indication Under Review: in adults for the treatment of idiopathic pulmonary fibrosis (IPF).

SMC Restriction: For use in patients with a predicted forced vital capacity (FVC) >80%

Nintedanib, compared with placebo, reduces the decline in pulmonary function assessed by FVC in patients with IPF.

This advice applies only in the context of approved NHSScotland Patient Access Scheme (PAS) arrangements delivering the cost-effectiveness results upon which the decision was based, or PAS/ list prices that are equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Nintedanib (Ofev®) has previously been accepted for restricted use in adults with IPF with a predicted FVC ≤80% (SMC1076/15); this advice remains valid.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Nintedanib is a tyrosine kinase inhibitor (TKI) that blocks vascular endothelial growth factor receptors (VEGFR) 1-3, fibroblast growth factor receptors (FGFR) 1-3 and platelet-derived growth factor receptors (PDGFR) α and β kinase, thereby inhibiting the proliferation, migration and transformation to myofibroblast of lung fibroblasts which is associated in the pathogenesis of interstitial lung disease.[1, 2]

Nintedanib is administered orally at a dose of 150mg every 12 hours or 100mg every 12 hours in patients who do not tolerate the 150mg twice daily dose.[2]

1.2. Disease background

Idiopathic pulmonary fibrosis is a chronic disease that is associated with progressive fibrosis of the interstitium of the lung causing a decline in lung function and worsening dyspnoea. The prognosis is poor and median survival from diagnosis without treatment is 2 to 5 years; most patients die from respiratory failure. The rate of disease progression varies between patients, with some having relatively stable disease while others experience a rapid decline. Acute exacerbations of IPF can also occur and may be fatal for some patients.[1, 3, 4]

1.3. Company proposed position

In patients with a predicted FVC greater than 80%. SMC has previously accepted nintedanib for restricted use in adults with IPF with a predicted forced vital capacity (FVC) less than or equal to 80% (SMC1076/15).

1.4. Treatment pathway and relevant comparators

Clinical guidelines recommend a combination of pharmacological and non-pharmacological interventions for the treatment of IPF. Antifibrotic therapies, nintedanib and pirfenidone are both licensed and recommended for use in patients with IPF. However, in NHS Scotland these treatments are restricted for use in patients with a predicted FVC less than or equal to 80% (SMC1076/15 and SMC835/13). Non-pharmacological interventions include best supportive care and pulmonary rehabilitation for appropriate patients. Best supportive care should be offered from diagnosis and can include management of underlying comorbidities such as pulmonary hypertension, gastroesophageal reflux and obstructive sleep apnoea, management of symptoms including breathlessness and the requirement for oxygen therapy, cough, anxiety and palliative care. Selected patients at increased risk of mortality may be suitable for lung transplantation. Enrolment in clinical studies should be considered at all stages.[3, 5] The most relevant comparator for the indication and the positioning under review is best supportive care.

1.5 Category for decision-making process

Nintedanib meets SMC orphan equivalent criteria

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of nintedanib for this indication comes from the INPULSIS-1, INPULSIS-2 and TOMORROW studies, and their subsequent open-label extension studies.

Table 2.1. Overview of relevant studies

Criteria	INPULSIS-1 and -2[1, 6]	TOMORROW[1, 4]
Study Design	Identically designed randomised, multicentre, double-blind phase III studies.	Randomised, multicentre, double-blind phase II study.
Eligible Patients	• Aged ≥40 years with a diagnosis of IPF according to standard guidelines <5 years before screening. • High-resolution computed tomography (HRCT) <1 year before randomisation and lung-biopsy (if available) reviewed centrally by a single radiologist and a single pathologist to confirm diagnosis. • FVC ≥50% predicted and a diffusion capacity of the lung for carbon monoxide (DL_{CO}) 30% to 79% predicted.	
		• Partial pressure of arterial oxygen (PaO_2) ≥55mmHg at altitudes up to 1500m or ≥50mmHg at altitudes above 1500m.
Treatments	Nintedanib 150mg twice daily orally or placebo for 52 weeks. Dose reductions to 100mg twice daily were permitted to manage adverse events. Concomitant therapy with prednisolone up to 15mg or equivalent was permitted if the dose was stable for ≥8 weeks before screening. After 6 months of study treatment, azathioprine, cyclophosphamide, cyclosporine, N-acetylcysteine, or >15mg prednisone daily or the equivalent was permitted at the discretion of the investigator if condition worsened.	Nintedanib 50 mg once daily, 50 mg twice daily, 100 mg twice daily, 150 mg twice daily orally or placebo for 52 weeks. Concomitant therapy with prednisolone up to 15mg or equivalent was permitted if the dose was stable for ≥8 weeks before screening. Only results from comparisons with the licensed dose, 150mg twice daily will be discussed in the DAD.
Randomisation	Randomised in a 3:2 ratio	Equal randomisation to each group
Primary outcome	The annual rate of decline in FVC (mL per year)	
Secondary outcomes	• Change from baseline in the total score on the St Georges Respiratory Questionnaire (SGRQ) at 52 weeks • Time to the first acute IPF exacerbation (investigator assessed) at 52 weeks • Overall survival	• Overall survival
Statistical analysis	A hierarchical statistical testing strategy was applied in the study with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Outcomes were tested in the following prioritised order: annual decline in FVC, change SGRQ total	A closed loop testing procedure was used for the primary analysis of the primary outcome.

	score and time to first acute IPF exacerbation.	

The results from the primary and key secondary outcomes from the INPULSIS studies have been reported in Table 2.2.

Table 2.2. Primary and secondary outcomes from the INPULSIS studies[1, 6]

	INPULSIS-1		INPULSIS-2	
	Nintedanib (n=309)	**Placebo (n=204)**	**Nintedanib (n=329)**	**Placebo (n=219)**
Primary outcome: Annual rate of decline in FVC				
Change in FVC (mL)	-114.7	-239.9	-113.6	-207.3
Difference, 95% CI	125.3 (77.7 to 172.8) p<0.001		93.7 (44.8 to 142.7) p<0.001	
Selected secondary outcomes measured at week 52				
Change in SGRQ total score	4.34	4.39	2.80	5.48
Adjusted difference, (95% CI)	-0.05 (-2.50 to 2.40)		-2.69 (-4.95 to -0.43) p=0.02	
Acute exacerbations*	6.1%	5.4%	3.6%	9.6%
Time to first exacerbation HR, 95% CI	1.15 (0.54 to 2.42)		0.38 (0.19 to 0.77), p=0.005	
CI=confidence interval; FVC=forced vital capacity; HR = hazard ratio; SGRQ = St George's Respiratory Questionnaire total score (range 0 to 100, with higher scores indicating poorer quality of life). *patients reporting at least one (investigator-assessed) acute IPF exacerbation				

In a pre-specified pooled survival analysis of the INPULSIS studies, all-cause mortality occurring within 52 weeks was numerically lower in the nintedanib group compared with placebo however the difference was not significant; 5.5% versus 7.8%.[6]

Results for the primary and selected secondary outcomes from the TOMORROW study have been presented in Table 2.3 for nintedanib 150mg twice daily compared with placebo.

Table 2.3 Primary and selected secondary outcomes from the TOMORROW study[1, 4, 7]

	Nintedanib (n=86)	**Placebo (n=87)**
Primary outcome: Annual rate of decline in FVC		
Change in FVC (mL)	-60	-191
Difference, 95% CI	131 (27 to 235) p=0.0639[A]	
Selected secondary outcomes measured at week 52		
Change in SGRQ total score	-0.66	5.46
Adjusted difference	-6.12	
Acute exacerbations*	2.3%	14%
CI=confidence interval; FVC=forced vital capacity; SGRQ = St George's Respiratory Questionnaire total score (range 0 to 100, with higher scores indicating poorer quality of life). *patients reporting at least one (investigator-assessed) acute exacerbation [A]Difference was statistically significant when a less stringent pre-specified hierarchical testing procedure was used; nominal p-value=0.0136		

In an analysis using pooled data from the INPULSIS studies and the TOMORROW study, the adjusted annual rate of decline in FVC was -112.4mL/year in the nintedanib group and -223.3mL/year in the placebo group (adjusted between group difference of 110.9mL/year). The hazard ratio (HR) for time to first investigator-reported acute exacerbation at 52 weeks was 0.53 (95% CI: 0.34 to 0.83). All-cause mortality was 5.8% (42/723) and 8.3% (42/508) in the nintedanib and placebo groups respectively at 52 weeks.[8]

2.2. Evidence to support the positioning proposed by the submitting company

A post hoc subgroup analysis using pooled data from the INPULSIS studies was conducted to support the proposed positioning in patients with a FVC>80% predicted. In the FVC >80% (n=485), the adjusted mean difference between nintedanib and placebo for annual rate of FVC decline was 128.4mL (95% CI: 78.0 to 178.8).[9] The HR for time to first acute exacerbation was 0.49 (95% CI: 0.17 to 1.35) and the between group difference in the adjusted mean change from baseline in SGRQ total score was -1.07 (95% CI: -3.45 to 1.32). Subgroup interaction analysis were not significant for the outcomes reported between the FVC >80% and FVC ≤80% predicted subgroups.[10]

2.3. Supportive studies

INPULSIS-ON was an open-label extension study that assessed the long-term safety of nintedanib in 734 patients who had completed the INPULSIS studies. The median total exposure to nintedanib in INPULSIS and INPULSIS-ON combined was 44.7 months. From baseline to week 192, the adjusted mean rate of decline in FVC was -135.1mL per year in all patients during INPULSIS-ON (-145.0mL per year in those who continued nintedanib and -119.7mL per year in those who initiated nintedanib), the adjusted mean change in FVC was -327.2mL, the adjusted rate of acute exacerbations was 5.6 per 100 patient-years and 188 patients died over approximately 5 years of follow-up.[11]

The open-label extension of the TOMORROW study included 35 patients who had received nintedanib 150mg twice daily with a mean total exposure during the phase II and extension study of 54 months. In this treatment group, the adjusted annual rate of decline in FVC was -134.8mL per year. Analyses including data from the phase II and open-label extension from 85 patients initially randomised to nintedanib 150mg twice daily indicated an adjusted annual rate of decline in FVC of -125.4mL per year and 22 patients died.[12]

2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

The submitting company presented an indirect treatment comparison which has been used to inform the economic analysis.

Table 2.4. Summary of indirect treatment comparison

Criteria	Overview
Design	Bayesian network meta-analysis (NMA)
Population	Adult patients with IPF
Comparators	Placebo
Studies included	INPULSIS-1[6], INPULSIS-2[6] and TOMORROW[4] SP2[13], CAPACITY1 and 2[14], SP3[15], ASCEND[16], PANTHER-IPF[17], Homma et al[18].
Outcomes	• Acute exacerbation of IPF • Loss of lung function (decline in predicted FVC ≥10%) • Serious cardiac adverse events • Serious gastrointestinal adverse events • Overall discontinuation
Results	The results from the NMA suggest that nintedanib may be superior to placebo for exacerbations of IPF and loss of lung function and inferior for serious gastrointestinal adverse events and overall discontinuation. There is no evidence to suggest a difference between the groups for serious cardiac events.

Company conclusion	No conclusions are explicitly stated for the NMA results in this submission.

3. Summary of Safety Evidence

The safety profile of nintedanib is associated with gastrointestinal (GI) toxicity, especially diarrhoea and there is also an increased risk of liver toxicity. The regulator concluded that most adverse events (AEs) were manageable with dose reductions.[1]

Pooled data from the phase III studies INPULSIS-1 and -2 at week 52 indicate that the majority of patients in both the nintedanib and placebo groups reported an AE: 96% (609/638) and 90% (379/423), respectively and were considered treatment-related in 71% and 28%. In both groups, 30% of patients reported a serious adverse event and AEs leading to treatment discontinuation in each group were 19% and 13%.[1]

Nintedanib was associated with a higher rate of GI adverse events than placebo, 77% versus 40%; diarrhoea was the most common (62% versus 18%) and was mainly reported as mild to moderate in intensity. More patients in the nintedanib group discontinued treatment due to GI AEs compared with placebo (7.4% versus 1.2%). Nintedanib is also associated with a potential for hepatic adverse events and elevated liver enzymes while on treatment. Other potentially serious AEs include myocardial infarction, hypertension, bleeding and GI perforation.[1, 2, 6]

No new safety signals were identified in the INPULSIS-ON open-label extension study with data for up to 68 months of treatment. The most frequently reported AE was diarrhoea (71% [519/734]) which resulted in treatment discontinuation in 5% of patients who continued nintedanib and 10% in patients who initiated nintedanib in the extension study. In each of the nintedanib groups, the event rate (per 100 patient treatment years) for major cardiovascular events was 3.6 and 2.4. See the SPC for further safety information.[2, 11, 19]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Nintedanib reduced the rate of decline in FVC by 125.3mL per year in INPULSIS-1 and by 93.7mL per year in INPULSIS-2, the results were statistically significant and described by the regulator as showing a clear and consistent benefit. The results from the TOMORROW study were consistent with a reduction in the rate of FVC decline of approximately 131mL per year with nintedanib, but statistical significance was not reached for the primary analysis.[1, 4, 6]
- The results from a pooled post-hoc subgroup analyses from the INPULSIS studies support the proposed positioning and indicated a 128.4mL per year reduction in the rate of decline in FVC in patients with a FVC>80% predicted.
- The results from the open-label extension studies, INPULSIS-ON and TOMORROW, suggest that the reduction in the rate of annual decline in FVC is maintained beyond 4 years.[11, 12]

4.2. Key uncertainties

- Statistically significant improvements were reported with nintedanib for key secondary outcomes, change in SGRQ total score and time to first exacerbation in INPULSIS-2 but not in INPULSIS-1. The reason for the inconsistency between results in the two studies is uncertain; the number of acute exacerbations in each study was relatively low and the regulatory report suggested that one explanation for the discrepancy in the quality of life outcome (SGRQ total score) could have been the increased toxicity and burden of treatment associated with nintedanib. In the TOMORROW study, numerical improvements in the SGRQ total score and exacerbation rate were observed.[1, 4, 6]
- Data to support the proposed positioning is from a pooled post hoc subgroup analysis of the INPULSIS studies which was not pre-planned or powered to detect differences between groups, therefore the results should be interpreted with caution.
- The economic analysis was informed using some estimates from the NMA. However, direct comparative evidence for nintedanib and placebo is available from the INPULSIS and TOMORROW studies. Furthermore, the population in the NMA is wider than the proposed positioning in patients with a FVC >80% predicted. Other limitations included heterogeneity in patient characteristics and differences and lack of definitions for some outcomes and the time frame over which they were assessed. The results from the NMA seem reasonable, but due to the limitations, the company has provided alternative scenarios for the economic analysis in patients with a FVC >80% predicted which better reflects the proposed positioning.
- Randomised controlled evidence for nintedanib in IPF is limited to one year. The extension studies provide longer-term evidence, however, the open-label single-arm study design may bias subjective efficacy and safety outcomes and prevents analysis with a relevant comparator. These studies may also be prone to selection bias with patients who performed well in the randomised study more likely to enter the extension study and remain on treatment for longer, which could hamper the interpretation of survival data which has been used in the economic analysis.
- FVC is not a direct health outcome and has been used as a surrogate for other direct outcomes such as mortality. A pooled analysis in patients with fibrosing interstitial lung diseases suggested that slowing the rate of FVC decline reduces the risk of death.[20] Results from a pooled analyses of the INPULSIS studies indicated a numerically lower mortality rate at 52 weeks in the nintedanib group compared with the placebo group (5.5% versus 7.8%) and in INPULSIS-ON, 188 patients died over approximately 5 years. However these results are descriptive only and are subject to bias and uncertainty as described above.[6, 11]

4.3. Clinical expert input

Clinical experts consulted by SMC considered that nintedanib filled an unmet need for the treatment of IPF in patients with a predicted FVC >80% as there are no antifibrotic treatments currently approved for use in Scotland for this patient population. They indicated that it was a therapeutic advancement due to the favourable results for nintedanib from the INPULSIS and TOMORROW studies in slowing the progression of IPF and because it would allow the earlier

introduction of therapy for appropriate patients. Clinical experts intimated that they would like this medicine to be available to all eligible patients, regardless of predicted FVC levels which is not always truly reflective of the severity of a patient's condition.

4.4. Service implications

Additional respiratory clinical resource may be required, in particular respiratory nurse and pharmacist specialists, to manage prescribing and to monitor and treat potential side effects.

5. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of nintedanib, as an orphan-equivalent medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Idiopathic pulmonary fibrosis is a rare and devastating disease with no cure. The progressive symptoms, particularly breathlessness have a significant impact on quality of life causing severe disability and loss of independence.
- There is a high unmet need for an effective treatment in patients with an FVC >80% predicted as supportive therapies are the only current options. PACE clinicians described how they have to wait for a patient's condition to deteriorate to an FVC ≤80% predicted before they can offer antifibrotic treatment. If approved, nintedanib would be the first antifibrotic available in Scotland for this cohort of patients.
- Nintedanib has been shown to slow disease progression by decreasing the rate of FVC decline and reducing exacerbations, it may also extend life. This could allow patients to remain active and independent for longer and reduce the potential care burden for caregivers.
- Nintedanib is an oral treatment which is convenient to take. It is generally well tolerated; gastrointestinal side effects are common but usually manageable.
- PACE participants considered that the place in treatment should be as per the licensed indication which includes patients with an FVC >80% predicted.

Additional Patient and Carer Involvement

We received a patient group submission from Action for Pulmonary Fibrosis, which is a registered charity. Action for Pulmonary Fibrosis has received 1% pharmaceutical company funding in the past two years, including from the submitting company. A representative from Action for Pulmonary Fibrosis participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case, as described in table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	50 years/lifetime
Population	Adult IPF patients who present an FVC >80% predicted at diagnosis
Comparators	Nintedanib was compared to BSC alone
Model description	A Markov model with seventeen mutually exclusive health states is presented. There are eight states based on 10-point decreases in predicted FVC % that patients can experience with or without having had an acute exacerbation and one death state. Patients can either remain at their current FVC % health state or decline, with patients who have experienced an exacerbation having a greater probability of decline in FVC. In the original submission, patients who decline below a predicted FVC of 40 would be expected to die; this feature is turned off in the model base case as it was expected to double count deaths already included in the OS curve.
Clinical data	TOMORROW (Phase II) trial and its open-label extension and the INPULSIS-1 and INPULSIS-2 (Phase III) trials, and their subsequent open-label extension INPULSIS-ON.
Extrapolation	Survival was modelled in both treatment arms by log-logistic curves derived from pooled trial data (TOMORROW, INPULSIS 1, 2 and ON). This was entirely independent of health state, an assumption validated by the submitting companies' analysis. Clinically important AEs (GI perforation and diarrhoea) were also based on the pooled trial data. Transition probabilities, discontinuation, utility values and serious AEs (cardiac event and GI event) were informed by a Bayesian NMA previously conducted to support the original submission to SMC (SMC 1076/15) using INPULSIS 1 and 2[6].
Quality of life	Health benefits were measured in QALYs. These were collected directly in the INPULSIS trials[6] through EQ-5D-3L. Health state utility was stratified in the model by lung function, with a separate initial one-time and permanent decrement applied to patients who experienced an acute exacerbation. One-time disutilities from serious GI events were also based on analysis of INPULSIS trials data whilst one-time disutilities for serious cardiac events, GI perforation and mild-moderate diarrhoea were derived from a UK database study, for use when condition-specific data are not available.[21]
Costs and resource use	Resource use was taken from a retrospective analysis of INPULSIS trials for 1,014 patients[22]. From this data the probability, number of occasions and intensity/duration of occasions was taken and multiplied by an externally sourced unit cost to obtain cost by health state. An exception to this was liver function tests which was assumed to be performed on all patients receiving nintedanib every cycle (3 months). Costs for these all of these resources were taken from acceptable published sources and inflated to 2020/21 values.[23]
PAS	A PAS was submitted by the company and assessed by PASAG as acceptable for implementation in NHSScotland. Under the PAS, a simple discount was offered on the list price.

BSC, best supportive care; IPF, idiopathic pulmonary fibrosis; FVC, forced vital capacity; QALY, quality-adjusted life-year; PAS, patient access scheme; PASAG, patient access scheme assessment group; GI, gastro-intestinal; NMA, network meta-analysis; AE, adverse event.

6.2. Results

The submitting company's main economic results are given in Table 6.2. These results apply no treatment cost to the comparator arm treatment. The results presented do not take account of the PAS for nintedanib but this was included in the results used for decision-making. SMC is unable to present the results using the PAS for nintedanib due to confidentiality issues.

The main driver of incremental costs was additional medicine acquisition costs of nintedanib compared to BSC and patient monitoring and oxygen use costs. The main driver of incremental QALY benefit came from the additional survival for patients on nintedanib.

Table 6.2 Base-case results (list price)

Technologies	Total costs	Total LYG (discounted)	Total QALYs	Inc. costs	Inc. LYG (discounted)	Inc. QALYs	ICER (£/ QALY)
Original base case results							
Nintedanib	£89,235	7.40	5.70	-	-	-	-
BSC	£19,262	4.08	3.21	£69,973	3.32	2.49	28,118
ICER, incremental cost-effectiveness ratio; LYG, life year gained; PAS, Patient Access Scheme; QALY, quality-adjusted life year							

6.3. Sensitivity analyses

The submitting company performed a probabilistic sensitivity analysis (PSA), one-way sensitivity analysis (OWSA) and scenario analysis.

The sensitivity of key drivers of cost-effectiveness was explored with a one-way sensitivity analysis. Discontinuation and mortality had the most significant impact, but no single variation had a major impact on the ICER.

A further 24 scenarios were ran to test model parameters/assumptions. A shorter time horizon of 5 years raised the ICER substantially suggesting the cost-effectiveness of nintedanib is strongly based on survival data predictions. Results of this scenario varying the time horizon, along with scenarios requested from the submitting company, can be found in table 6.3.

Table 6.3 Tests on other model parameters (list price)

Parameter	Description of parameter varied	ICER (£/IQALYs)
Scenarios provided in the company's submission		
Base case		£28,118
Shorter time horizons	Time horizon of 5 years	£101,135
	Time horizon 10 years	£45,124
Requested scenarios		
General population mortality	Apply general population mortality when it exceeds OS curve predicted IPF mortality	£30,483
Using FVC >80% pred subgroup data to inform inputs	Using subgroup data to inform log-logistic OS models	£22,326
	Using subgroup data to inform Weibull OS models	£24,075

	Using subgroup data to inform lognormal OS models	£28,510
	Transition probabilities for FVC predicted >80%	£27,648
	Transition probabilities for FVC predicted >80% and OR for NDB in patients with FVC predicted >80% (OR=0.50)	£27,577
	Treatment discontinuation and loss of lung function with base-case OR=0.54 for loss of lung function applied to nintedanib	£33,805
	Treatment discontinuation and loss of lung function with OR=0.50 for loss of lung function applied to nintedanib	£33,706
Combined scenario	• Use general population mortality • Use overall survival derived from the subgroup with FVC >80% predicted • Use loss of lung function transition probabilities derived from the subgroup with FVC >80% predicted • Use odds ratio (OR) for loss of lung function derived from the subgroup with FVC >80% predicted • Use treatment discontinuation derived from subgroup of patients with baseline FVC >80% predicted	£29,304
Nintedanib vs watchful waiting	watchful waiting nintedanib (log-logistic)	£25,966
	watchful waiting pirfenidone (log-logistic)	£27,511
	watchful waiting nintedanib (Weibull)	£28,430
	watchful waiting pirfenidone (Weibull)	£27,039

6.4. Key strengths

- A key strength of this submission is the trial data. Despite the condition being relatively rare the data available are from well populated, long studies. Sufficient relevant subgroup FVC data are available from these studies to obtain efficacy, survival, and discontinuation values for the model, as was requested of the submitting company as a scenario analysis. Furthermore, large quantities of resource use data were also available from the INPULSIS studies allowing both the efficacy and resource use data to be mostly directly informed by the relevant studies.
- The model was well constructed and easy to understand with health states that are comprehensive and granular enough to capture relevant costs and QALY differences.

6.5. Key uncertainties

- The largest uncertainty is the exclusion of nintedanib and pirfenidone from BSC patients who fall below a predicted FVC of 80%. This exclusion makes it unclear whether nintedanib without the threshold limitation would be cost-effective versus current clinical practice. Implementing this into the model may increase cost-effectiveness, as BSC arm patients who switch will accrue the treatment costs of nintedanib, whilst being in a lower average health state and experiencing poorer survival outcomes prior to treatment initiation.

Nevertheless, this change to the model could also decrease cost-effectiveness, as patients in the BSC arm can avoid initial treatment costs from nintedanib. The submitting company has now provided comprehensive scenario analyses, demonstrating the impact on ICERs of nintedanib administered to patients with an FVC % > 80% versus watchful waiting for both nintedanib and pirfenidone. The ICER for the scenarios comparing nintedanib to watchful waiting is lower than nintedanib versus BSC, as can be seen in table 6.3.

- A limitation of the open-label extension overall survival data is selection bias. The company has responded to a request asking if this could be addressed by applying BSC OS curves to patients who discontinue in the treatment arm. The company cited the validation work they have done against registry data to make the case that altering survival, using this method, would result in an LY difference of 0.9089 between NDB and BSC and this does not align to real-world data. A scenario based on this analysis was not provided. Comparison of the model nintedanib vs BSC survival difference to registry data provided reassurance the model predictions are broadly consistent with published estimates.
- Another uncertainty surrounds the mortality in the model. The company stated the time horizon to be lifetime, but the actual value used in the model is 50 years. Given the baseline starting age of 66.76 this should be more than enough to encompass the lifetime costs and QoL effects. By the final cycle 97.35% of patients in the nintedanib arm and 99.81% of patients in the BSC arm have died. The current method of survival applied is underestimating patient mortality in the long run. The company has provided a scenario applying general population mortality and this resulted in an ICER of £30,483.
- The model inputs for discontinuation, loss of lung function, exacerbation and overall survival remain informed by the whole population rather than the relevant FVC >80% predicted subgroup. To obtain greater certainty in decision making the subpopulation of interest should be used to inform the model. However, the scenarios provided by the company for parameter specific subgroup analysis (see table 6.3) indicate this is unlikely to have a significant impact on cost-effectiveness. The combined analysis, which uses subgroup data, if relevant/available, to source parameter inputs and applies general population mortality, resulted in an ICER of £29,304.

7. Conclusion

The Committee considered the benefits of nintedanib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as nintedanib is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted nintedanib for restricted use in NHSScotland.

8. Guidelines and Protocols

In 2017 the National Institute of Health and Clinical Excellence (NICE) produced clinical guideline, Idiopathic pulmonary fibrosis in adults: diagnosis and management (Guideline 163). These guidelines recommend offering best supportive care focused on information provision, symptom relief and management of co-morbidities. NICE acknowledge that there is limited evidence to show that pharmacological interventions increases the survival of people with IPD. Pirfenidone and nintedanib are recommended for people who have a forced vital capacity between 50% and 80% and that treatment is stopped if there is evidence of disease progression.[5]

The American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS) and Asociación Latinoamericana de Tórax (ALAT) have produced updated guidelines for IPF and Progressive Pulmonary Fibrosis in Adults in 2022.[3] These guidelines recommend pharmacological treatment with nintedanib or pirfenidone for patients with IPF. Recommended non pharmacological interventions include oxygen supplementation (if hypoxemic) and pulmonary rehabilitation. Symptom control (palliative care) is also recommended.

9. Additional Information

9.1. Product availability date

14 January 2015

9.2. Summary of product characteristics

See the SPC for further information including dosing and safety.

Nintedanib 100mg soft capsules (Ofev®) SPC

Nintedanib 150mg soft capsules (Ofev®) SPC

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Nintedanib	**150mg twice daily orally**	**26,100**

Costs from BNF online on 01/11/2022. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 1,009 patients eligible for treatment with nintedanib in each year. The estimated uptake rate was 20% in year 1 and 63% in year 5. This resulted in 202 patients estimated to receive treatment in year 1 rising to 636 patients in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 09 December 2022.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.