Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Professor Jonathan G Fox

nintedanib 100mg and 150mg capsules (Ofev®) SMC No. (1076/15)

Boehringer Ingelheim

4 September 2015

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 Scotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan process

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

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) less than or equal to 80%.

Nintedanib, compared to placebo, reduces the decline in pulmonary function assessed by forced vital capacity in patients with IPF.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of nintedanib. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

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

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

In adults for the treatment of idiopathic pulmonary fibrosis (IPF).

Dosing Information

150mg twice daily 12 hours apart. 100 mg twice daily is only recommended in patients who do not tolerate 150 mg twice daily. The capsules should be taken with food, swallowed whole with water, and should not be chewed or crushed. Dose reductions or interruption to manage adverse events are detailed in the summary of product characteristics. Treatment with nintedanib should be initiated by physicians experienced in the diagnosis and treatment of IPF.

Product availability date

13 April 2015

Nintedanib was designated as an orphan medicine for this indication on 26 April 2013.

Summary of evidence on comparative efficacy

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.[2] It is the second medicine (after pirfenidone) to be licensed for treatment of idiopathic pulmonary fibrosis (IPF) and has been designated an orphan medicinal product for the treatment of IPF.

Two double-blind phase III studies (INPULSIS-1 and -2) recruited patients aged at least 40 years, with a diagnosis of IPF in the preceding five years, who had a forced vital capacity (FVC) at least 50% of predicted and diffusion capacity of the lung for carbon monoxide (DL_{CO}) of 30% to 79%. The diagnosis of IPF was confirmed by central review by a single radiologist and a single pathologist of chest high resolution computed tomography (HRCT) within the previous year and (where available) lung biopsy, respectively. Patients were randomised in a 3:2 ratio to nintedanib 150mg orally twice daily or placebo for 52 weeks. The primary outcome, annual rate of decline in FVC, was assessed in all randomised patients who received at least one dose of study drug using a random coefficient regression model.

In both studies, the primary outcome measure was significantly reduced with nintedanib compared to placebo. The key secondary outcome, change from baseline to week 52 in St George's Respiratory Questionnaire (SGRQ) total score (in which higher scores indicate poorer quality of life), was significantly lower with nintedanib compared to placebo in INPULSIS-2, but not in INPULSIS-1. The other key secondary outcome of time to first acute exacerbation (investigator-assessed) was significantly longer with nintedanib in the INPULSIS-2 study, but not in INPULSIS-1. In a pre-specified pooled analysis of independently adjudicated data, the time to first acute exacerbation was significantly longer with nintedanib compared to placebo, with a hazard ratio (HR) of 0.32 (95% confidence interval [CI]: 0.16 to 0.65). The primary and key secondary results are summarised in the table.[1-6]

Table: Key results at 52 weeks from the INPULSIS-1 and 2 studies[1,2]

	INPULSIS-1		INPULSIS-2	
	Nintedanib	**Placebo**	**Nintedanib**	**Placebo**
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	
Exacerbations*	6.1% (19/309)	5.4% (11/204)	3.6% (12/329)	9.6% (21/219)
HR (95% CI) time to first	1.15 (0.54 to 2.42), p=0.67		0.38 (0.19 to 0.77), p=0.005	
Change in SGRQ total	4.34	4.39	2.80	5.48
Difference (95%CI)	-0.05 (-2.50 to 2.40), p=0.97		-2.69 (-4.95 to -0.43), p=0.02	

FVC = forced vital capacity; CI = confidence interval; 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.

Pre-specified analysis of pooled data from the INPULSIS-1 and -2 studies indicates that overall mortality at 52 weeks was lower in the nintedanib group compared to the placebo group: 5.5% versus 7.8%. However, the difference was not significant and analysis of time to death gave a HR of 0.70 (95% CI 0.43 to 1.12), p=0.14. Analyses of other survival endpoints, on-treatment mortality and respiratory mortality, had a consistent numerical advantage for nintedanib.[2,6]

A double-blind phase II study (TOMORROW) recruited patients to similar criteria as those in the INPULSIS studies, with the additional criterion of partial pressure of arterial oxygen (PaO2) of at least 55mmHg at altitudes up to 1500m or at least 50mmHg at altitudes greater than 1500m. Patients were randomised equally to 52 weeks' treatment with placebo, nintedanib 50mg once daily, nintedanib 50mg, 100mg or 150mg twice daily. The primary outcome, annual rate of decline in FVC (ml per year), was assessed in all randomised patients using only on-treatment data in a random effects mixed measures model with a closed test procedure. In the nintedanib 150mg twice daily (licensed dose) and placebo groups this was -60ml and -191ml per year, respectively, with a difference of -131ml per year (95% CI: 27 to 235). Using the pre-defined, multiplicity-corrected, closed testing procedure of primary endpoint analysis, this was not significant with p=0.0639. However, using the less stringent hierarchical method, which was a pre-defined sensitivity analysis, the difference was significant with p=0.0136.[1,6-8]

The secondary outcome, rate of acute exacerbation of IPF was significantly reduced with nintedanib 150mg twice daily compared to placebo: 2.3% (2/86) versus 13.8% (12/87), HR of 0.16 (95% CI: 0.04 to 0.71), p=0.0054. The adjusted mean change from baseline to week 52 in SGRQ was significantly improved with nintedanib 150mg twice daily compared to placebo for total score, -0.66 versus 5.46; symptoms domain, -3.14 versus 6.46; and in activity domain, 0.32 versus 7.48. There were non-significant reductions with nintedanib 150mg twice daily, compared to placebo, for all-cause mortality: 8.1% (7/86) versus 10.3% (9/87), HR 0.73 (95% CI: 0.27 to 1.98); and respiratory-related deaths (adjudicated by blinded committee), 2.3% versus 9.2%, HR 0.22 (95% CI: 0.05 to 1.06).[1,2,6,7] When these all-cause mortality data were pooled with the INPULSIS-1 and -2 studies, 5.8% (42/723) and 8.3% (42/508) of patients in the respective groups had died, and the HR was 0.70 (95% CI: 0.46 to 1.08), p=0.097.[9]

Summary of evidence on comparative safety

Pooled data from the phase III studies INPULSIS-1 and -2 indicate that most patients in both the nintedanib and placebo groups reported an adverse event: 96% (609/638) and 90% (379/423), respectively, which were defined as related-to-treatment in more patients within the nintedaninb group: 71% (455/638) and 28% (120/423), respectively. Across the nintedanib and placebo groups there were similar rates of severe adverse events, 27% and 23%; and serious adverse events, 30% and 30%, respectively. Adverse events leading to study discontinuation were higher in the nintedanib group compared to placebo: 19% (123/638) versus 13% (55/423).[1]

Nintedanib is associated with higher rate of gastrointestinal adverse events than placebo, 76% (488/638) versus 40% (168/423), with diarrhoea being the most common, 62% versus 18%, and others including nausea, 24% versus 6.6%; abdominal pain, 8.8% versus 2.4%; upper abdominal pain, 6.4% versus 3.5%; and constipation, 6.0% versus 4.0%. The rate of decreased weight reported as an adverse event was also higher with nintedanib compared to placebo, 9.7% versus 3.5%, respectively.[1]

Nintedanib is also associated with a potential for hepatic adverse events. Pooled data from the two phase III studies indicate that the proportion of patients who experienced elevation of liver enzymes from normal range at baseline to outside the reference range while on treatment was greater with nintedanib compared to placebo: 27% versus 7.2% for aspartate aminotransaminase; 21% versus 5.3% for alanine aminotransaminase; 15% versus 6.8% for alkaline phosphatase; 39% versus 10% for gamma glutamyl transferase; and 7.7% versus 5.3% for total bilirubin.[1]

Summary of clinical effectiveness issues

IPF is a rare disease characterised by progressive fibrosis of the lung interstitium, resulting in a progressive decline in lung function, usually leading to death due to respiratory failure. The rate of disease progression varies between patients, with some having relatively stable disease and others having a rapid decline. Acute exacerbations of IPF can also occur and may lead to death. The median overall survival across a range of studies is two to five years.[1,10,11] Treatment options are limited. For some patients a lung transplant can improve survival.[1] The first medicine licensed for IPF, pirfenidone, was accepted for restricted use by SMC in August 2013. It is licensed for adults with mild to moderate IPF and its use is restricted to those with predicted FVC less than or equal to 80%. Pirfenidone has been shown to reduce the decline in FVC and in a recently published analysis of pooled data from three pivotal phase III studies it was associated with a significant reduction in mortality.[12] Other treatments that have been used to treat IPF, including corticosteroids, immunosuppressants and N-acetylcysteine, are not licensed for IPF and their efficacy is uncertain. In a recently published study, N-acetylcysteine was no better than placebo for reducing the decline in FVC.[13] There is therefore an unmet need for treatment options for this condition.

In the two pivotal phase III studies and the licensed dose group in the phase II study, there was a significant reduction in the annual decline of FVC with nintedanib compared to placebo of approximately 100mL/year. There were divergent slopes of decline in FVC for the nintedanib and placebo groups, suggesting that benefit is continued over time.[1] The percent predicted FVC

outcome can reduce or eliminate variability in assessment of FVC due to demographic factors such as age, gender and body size. In the INPULSIS-1 and -2 studies, change in percent predicted FVC was consistent with the primary analyses of absolute change in FVC.[1,3]

FVC is not a direct health outcome and has not been verified as a surrogate for any direct health outcomes, such as mortality.[6] Changes in the rate of lung function decline may not be directly perceptible by patients.[1] Therefore, secondary outcomes in terms of benefits on quality of life and reduction in acute exacerbations are key data, relevant to patients. In INPULSIS-2, but not INPULSIS-1, and (with the licensed dose) in the TOMORROW study, there was a significant advantage for nintedanib compared to placebo for time to first acute exacerbation and change from baseline to week 52 in SGRQ.[3,5] The HR for time to first exacerbation was 0.38 (95% CI: 0.19 to 0.77) and 0.16 (95% CI: 0.04 to 0.71) in the INPULSIS-2 and TOMORROW studies, respectively. For SGRQ total score (which is assessed on a 0 to 100 scale), differences between nintedanib and placebo were 2.69 and 6.12 points in the respective studies. A minimal important difference for SGRQ total score in IPF has not been defined (in patients with chronic obstructive pulmonary disease it is 4 points). The clinical significance of effects on quality of life is unknown. In the individual nintedanib studies and pooled analyses, which were not powered to investigate overall survival, nintedanib was associated with a non-significant numerical advantage over placebo for overall survival. The analysis of data from the phase II and III studies gave a HR of 0.70 (95% CI: 0.46 to 1.08).[1-6,9]

In the INPULSIS studies, the dose of nintedanib could be reduced or interrupted as specified in the protocol to manage toxicity. This occurred more frequently in the nintedanib groups. However, a subgroup analysis by dose intensity, >90% or <90%, found that decline in FVC was similar in both groups and efficacy was not affected by dose reductions or interruptions.[9]

A limitation of the evidence is that the duration of the main phase II and III studies was one year, although patients could continue into extension studies, where mean duration of treatment was about 6 months. There are therefore few data on efficacy and safety beyond this. The studies also excluded patients with FVC less than 50%, so there are no data on efficacy and safety when pulmonary function has decreased below this level. There are also no direct comparative data relative to the only other medicine licensed for IPF, pirfenidone.

Bayesian network meta-analyses (NMA) compared nintedanib, pirfenidone and N-acetylcysteine for overall survival, acute exacerbation of IPF, loss of lung function (decline in percent predicted FVC ≥10%), serious cardiac and gastrointestinal adverse events, and overall discontinuation. Data were included from 10 studies and results in the form of odds ratios (OR) for each drug relative to placebo were applied to the economic analyses. There were some weaknesses that limit the validity of the results including the quality of input data and heterogeneity in definition of outcomes or analyses of these and time-frames over which they were assessed. Also, for some outcomes there were inconsistencies between the results of the NMA and published evidence.

Clinical experts consulted by SMC advised that effective treatment options for IPF are limited. Pirfenidone is used, according to SMC advice, in patients with FVC less than or equal to 80% but there remains an unmet need for a treatment that can be commenced earlier in the disease process, to prevent decline. Pirfenidone and nintedanib have different modes of action and tolerability profiles.

Summary of patient and clinician engagement

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 medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Idiopathic pulmonary fibrosis (IPF) causes a progressive loss of lung function, with increasing symptoms, disability and oxygen dependence. Median survival without treatment is less than three years from diagnosis. As the disease progresses, patients become more breathless and need help with all aspects of daily living.

- The main treatment currently available, pirfenidone, has evidence of similar efficacy to nintedanib but not all patients respond to it or can tolerate the side effects. Clinicians suggested that around 20% of patients may be unable to tolerate pirfenidone, compared to an estimated 5% of patients who would be unable to tolerate nintedanib. Having a further option with a different side effect profile and different mechanism of action would be helpful.

- Pirfenidone has been accepted by SMC for restricted use in patients whose FVC is below 80%. Clinicians described that in practice they need to wait for patients to deteriorate before they can use pirfenidone. Nintedanib has been shown to reduce the decline in lung function for patients regardless of baseline FVC and to increase the time to first exacerbation. This benefits patients physically and psychologically and preserves their lung function for longer.

- IPF can be punctuated by acute exacerbations which are associated with a mortality of >50%; pirfenidone does not address these but nintedanib has been shown to reduce their occurrence.

- The PACE group reported that nintendanib has efficacy across the spectrum of patients with IPF, in contrast to pirfenidone. Although there may be a place for nintedanib use in patients who are intolerant of pirfenidone, clinicians felt that there is no clear rationale for restricting it to second-line use. Given that all patients with IPF could potentially benefit, clinicians felt that it should be considered as a first line option alongside pirfenidone. Nintedanib may also be the only option for some patients. It has a better side effect profile and can also delay the time to first acute exacerbation.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis of nintedanib for the treatment of IPF. The main comparator in the analysis is pirfenidone, which was selected on the basis that it is the only accepted active treatment for IPF. Additional analyses were presented comparing nintedanib with best supportive care (BSC) and N-acetylcysteine (NAC) as secondary comparators, which the company noted may be relevant options for patients with an FVC >80% (i.e. those outwith the SMC restriction for pirfenidone).

A lifetime Markov model was used which was designed to capture disease progression over time as a combination of both lung function (through changes in FVC % predicted) and exacerbations. Health states were classified according to FVC % predicted with a range of 10% defining each health state. Transitions between the FVC % predicted health states were assessed according to the 3-month cycle length, where patients could remain in the same health state, transition to a lower FVC % predicted health state, and/or experience an exacerbation. It was assumed that once patients progressed to a worse health state it was not possible to subsequently move to better health states. Mortality was also included in the model.

The clinical data used in the model were taken from the two nintedanib clinical studies (INPULSIS) and the NMA. The baseline risks of mortality, disease progression, and acute exacerbations were derived from patient-level data from the placebo arm of the INPULSIS studies, which was assumed to be a proxy for BSC in the model. The company noted a range of concomitant treatments were allowed in the INPULSIS studies which would constitute BSC in practice. The relative effectiveness of nintedanib, pirfenidone and NAC were then estimated by applying the OR from the NMA to the baseline risks and assuming a constant relationship over time. It should be noted that the results of the NMA showed there were no significant differences between nintedanib and pirfenidone for any of the outcomes, but the numerical differences were included in the economic analysis.

The utility values were derived from patient-reported EQ-5D data from the INPULSIS studies. The utility values ranged from 0.838 for patients with FVC % predicted of 90 and above, to 0.6634 for patients with FVC% predicted of 40-49.9. Disutilities were then applied to these values to capture quality of life loss due to exacerbations and adverse events.

The analysis included drug costs of nintedanib, pirfenidone and NAC, but no drug costs were included in the BSC arm. The costs of concomitant medications were also included based on the rates observed in the pivotal studies. All treatments in the analysis are oral and therefore no administration costs were included. A patient access scheme (PAS) is in place for pirfenidone and the analysis used an estimate of the PAS price of pirfenidone. Other resource use included a range of tests and procedures, monitoring costs, hospital stays, follow-up costs, oxygen use, exacerbation costs, and end of life costs.

A PAS was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was offered. With the PAS, nintedanib was estimated to dominate pirfenidone i.e. was more effective and cost-saving. Cost-effectiveness analysis results for the comparisons with BSC and NAC were provided but cannot be published as the submitting company has indicated they are commercial in confidence.

A number of sensitivity analyses were provided and these showed that for the analysis versus pirfernidone, nintedanib remained the dominant treatment in all scenarios except when different NMA results were used where the incremental cost-effectiveness ratio (ICER) increased to between £3k and £4k. For the comparison with NAC and BSC, the results were particularly sensitive to the overall survival estimates and extrapolation approaches with the ICER varying through a wide range when the 95% confidence intervals were used.

The following limitations were noted:

- The base case analysis included QALY gains based on numerical differences in efficacy and safety derived from the NMA. A revised analysis which removed these differences was subsequently provided and this showed nintendanib remained the dominant treatment

versus pirfenidone. However, this analysis still assumed an incremental benefit with nintedanib in terms of acute exacerbations and loss of lung function, which is not supported by the NMA. When no difference in efficacy was assumed, nintedanib was a cost-effective treatment option.

- In the cost-utility analysis, the results were particularly sensitive to changes in overall survival with different extrapolation approaches resulting in large changes in the ICER. This highlights the uncertainty in the results. For the comparison with BSC, using the 95% confidence interval values resulted in the ICER varying through a wide range. Similarly, the results were sensitive to using difference overall survival extrapolation methods.
- The comparison with NAC may lack face validity as the QALYs estimated in the NAC arm of the model are less than BSC due to the NMA showing an improvement in overall survival with BSC vs NAC. However, this analysis is particularly uncertain.
- The utility values used in the analysis appear to lack face validity, particularly in the more severe health states where quality of life remains relatively high. The company highlighted this may be a result of the lack of sensitivity associated with the EQ-5D instrument in more severe health states. An additional analysis was provided using disease-specific SGRQ data but this resulted in similar utility values to those used in the base case analysis.

The Committee considered that the additional analyses presented comparing nintedanib with best supportive care (BSC) and N-acetylcysteine (NAC) were insufficiently robust to support its acceptance in line with the licensed indication. Nintedanib could therefore be considered only in the population of patients with FVC less than or equal to 80%.

The Committee also considered the benefits of nintedanib in the context of the SMC decision modifiers 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, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted nintedanib for restricted use in NHS Scotland.

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

Summary of patient and public involvement

The following information reflects the views of the specified Patient Groups.

- Submissions were received from the Pulmonary Fibrosis Trust and Action for Pulmonary Fibrosis, which are both registered charities.

- Action for Pulmonary Fibrosis has received pharmaceutical company funding in the past two years, including from the submitting company. The Pulmonary Fibrosis Trust has not received any funding from pharmaceutical companies in the past two years.

- Idiopathic pulmonary fibrosis (IPF) is a distressing, terminal, progressive illness that limits physical activity due to increasing breathlessness. The psychological burden of knowing that there is no cure is difficult for patients and their families. As a consequence of the progressive breathlessness associated with the disease, many patients experience anxiety and depression. As the disease progresses, patients' exercise capacity reduces and they

become breathless at rest, with even talking and eating requiring the use of supplementary oxygen. Patients will need help with activities of daily living such as washing, dressing and eating.

- The main treatment currently available to patients, pirfenidone requires regular blood tests for monitoring and the use of high factor sun block to combat one of the side effects. Not all patients can use this treatment.

- There is evidence that nintedanib can slow the progression of IPF and this would be important in improving patients' quality of life. It would give patients who cannot take pirfenidone another treatment option that may have more tolerable side effects.

Additional information: guidelines and protocols

The National Institute for health and Care Excellence (NICE) published Clinical Guideline CG163 on the diagnosis and management of suspected idiopathic pulmonary fibrosis in June 2013.[14] The guideline recommends against the use of the following medicines either as monotherapy or in combination for treatment of IPF: ambrisentan; azathioprine; bosentan; co-trimoxazole; mycophenolate mofetil; prednisolone; sildenafil; and warfarin. For guidance on the use of pirfenidone in IPF, the guideline refers to NICE Technology Appraisal TA282, also published in April 2013 (review in progress).[15] TA282 recommends pirfenidone as a treatment option in IPF for patients with a FVC between 50% and 80% predicted if the manufacturer provides pirfenidone with the discount agreed in the patient access scheme. Discontinuation of pirfenidone is recommended if there is evidence of disease progression (percent predicted FVC declines by 10% or more within any 12-month period).

In 2011 an official statement was issued by the American Thoracic Society (ATS), the European Respiratory Society (ERS), the Japanese Respiratory Society (JRS) and the Latin American Thoracic Association (ALAT) on IPF: evidence based guidelines for diagnosis and management. This notes that the committee felt that the preponderance of evidence to date suggests that pharmacologic therapy for IPF is without definitive, proven benefit and makes recommendations of varying strengths against most therapies. The recommendation against the use of the following medicines is strong: corticosteroid monotherapy, colchicine, cyclosporine A, combined corticosteroid and immune-modulator therapy, interferon, bosentan and etanercept. The recommendation against the use of the following is weak, that is these therapies should not be used in the majority of patients with IPF, but may be a reasonable choice in the minority: combined N-acetylcysteine, azathioprine and prednisolone, N-acetylcysteine monotherapy, anticoagulation and pirfenidone.[11]

In 2008 the British Thoracic Society (BTS) in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society issued an interstitial lung disease guideline. This noted that best supportive care should be considered a specific and important treatment strategy in all patients with IPF. It is a proactive approach to symptomatic treatment and may include oxygen therapy, pulmonary rehabilitation, opiates, antireflux therapy, withdrawal of steroids and other immunosuppressants, early recognition of terminal decline and liaison with palliative care specialists. To date there is no therapy proven to improve survival or otherwise significantly modify the clinical course of IPF. As such, it is recommended that all patients be considered for recruitment to high quality clinical trials of therapy and/or for lung transplantation if appropriate. Prednisolone (tapering from 0.5mg/day to 10-20mg/day) with azathioprine

(2mg/kg, maximum 150mg/day) and N-acetylcysteine (600mg three times a day) has been shown to have a significantly better treatment effect than prednisolone and azathioprine alone. However, further studies are required and this regimen currently carries a weak recommendation. The BTS issued an update in November 2011 in response to the discontinuation of the triple-therapy arm of the PANTHER study when an interim analysis indicated increased morbidity and mortality compared to placebo. This recommends that new patients with definite IPF should not be initiated on a regimen containing prednisolone plus azathioprine. In patients with definite IPF already receiving combination prednisolone, azathioprine and N-acetylcysteine therapy, it is recommended that azathioprine therapy in particular should be withdrawn if there is evidence of disease progression (declining lung function). In patients established on triple therapy with 'stable' disease, the decision to withdraw should be on a case-by-case basis, but the threshold for withdrawing azathioprine from elderly patients should be low.[16]

Additional information: comparators

The main comparators are pirfenidone and N-acetylcysteine, although the latter is unlicensed and its use may decline in the future following the recent publication of the PANTHER study.[12]

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Nintedanib	**150mg twice daily**	**26,100**
Pirfenidone	801mg three times daily	26,100
N-acetylcysteine*	600mg three times daily	448

Doses are for general comparison and do not imply therapeutic equivalence. Costs from submission for nintedanib; from MIMS on 22 April 2015 for pirfenidone; and for N-acetylcysteine costs are an average from recent invoices in January 2015. Costs do not take account of any patient access schemes.
*Unlicensed for use in IPF

Additional information: budget impact

The submitting company estimated there would be 1,225 patients eligible for treatment in each year with an estimated uptake rate of 0% in year 1 rising to 18% (220 patients) in year 5. A discontinuation rate of 31% was assumed each year.

Without the PAS for either nintedanib or pirfenidone, the company estimated the gross medicines budget impact to be £0 in year 1 rising to £2.4m in year 5. The net medicines budget impact was estimated at £0 in all years as nintedanib and pirfenidone have the same list price.

The budget impact estimates submitted by the company reflect the population covered by the licensed indication.

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

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. European Medicines Agency. European public assessment report for Ofev, Committee for Medicinal Products for Human Use (CHMP) Assessment report, 20 November 2014.
2. Boerhinger Ingelheim, Summary of product characteristics for Ofev, 15 January 2015.
3. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. New Engl J Med. 2014; 370(22): 2071-82.
4. Richeldi L, Cottin V, Flaherty KR, et al. Design of the INPLUSIS trials: two phase 3 trials of nintedanib in patients with idiopathic pulmonary fibrosis. Resp med 2014; 108: 1023-30.
6. US Food and Drug Administration. Medical review of nintedanib.
7. Richeldi L, Costabel U, Selman M, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. New Engl J Med. 2011; 365(12): 1079-87.
8. www.clinicaltrials.gov. record for TOMORROW study, NCT00514683, accessed 30 April 2015
9. US Food and Drug Administration. Statistical review of nintedanib
10. Meltzer EB, Noble PW. Idiopathic pulmonary fibrosis. Orphanet J Rare Dis. 2008; 3: 8.
11. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011; 183(6): 788-824.
12. King TE, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 2014; 370(22): 2083-92.
13. Martinez FJ, de Andrade JA, Anstrom KJ, et al. Idiopathic Pulmonary Fibrosis Clinical Research Network. Randomized trial of acetylcysteine in idiopathic pulmonary fibrosis. New Engl J Med. 2014; 370(22): 2093-101.
14. NICE clinical guideline 163. Idiopathic pulmonary fibrosis: the diagnosis and management of suspected idiopathic pulmonary fibrosis. Issued June 2013. Available at: https://www.nice.org.uk/guidance/cg163
15. NICE technology appraisal 282. Pirfenidone for treating idiopathic pulmonary fibrosis. Issued April 2013. Available at: http://www.nice.org.uk/guidance/ta282
16. Wells AU, Hirani N. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Thorax 2008; 63 Suppl 5: v1-58.

This assessment is based on data submitted by the applicant company up to and including 12 June 2015.

**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:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements

Drug 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 drug 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 NHS Scotland 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 NHS Scotland 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.