National Institute for Health and Care Excellence

Single Technology Appraisal

Nintedanib for treating idiopathic pulmonary fibrosis in people with a forced vital capacity above 80% predicted (part-review of technology appraisal guidance 379) [ID4062]

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Wording	Action for Pulmonary Fibrosis	Yes but the remit or scope should explain why NICE has not included patients with FVC under 50%, who currently denied antifibrotics once their FVC drops below 50% of expected? In Scotland there is no lower (50%) threshold.	Comment noted. TA379 final guidance outlines that drug treatment might not be appropriate for people with a percent predicted FVC of less than 50%. The committee concluded that in clinical practice nintedanib would be appropriate for treating people with a percent

Section	Stakeholder	Comments [sic]	Action
			predicted FVC of more than 50%.
	Boehringer Ingelheim	We agree with the inclusion of patients with a forced vital capacity (FVC) above 80% predicted in the scope. However, we would like to explore the possibility of including patients with FVC <50% predicted in the remit if it would be possible to withdraw the application for reimbursement in this population if it becomes clear during the appraisal that the recommendation in this group will be negative. If the above is possible, we suggest the following wording for the remit: "To appraise the clinical and cost effectiveness of nintedanib within its marketing authorisation for treating idiopathic pulmonary fibrosis in people with a forced vital capacity above 80% or below 50% predicted." If the above is not possible, we agree with restricting the remit to patients with an FVC >80% predicted, and suggest a small change as below: "To appraise the clinical and cost effectiveness of nintedanib within its marketing authorisation for treating idiopathic pulmonary fibrosis in people with a forced vital capacity above 80% predicted."	Comment noted. TA379 final guidance outlines that drug treatment might not be appropriate for people with a percent predicted FVC of less than 50%. The committee concluded that in clinical practice nintedanib would be appropriate for treating people with a percent predicted FVC of more than 50%. The title and remit of the scope have been updated to nintedanib for treating idiopathic pulmonary fibrosis in people with a forced vital capacity above 80% predicted.

Section	Stakeholder	Comments [sic]	Action
	British Thoracic Society	Yes this is a review that clinicians and patients alike have been campaigning for.	Comment noted. No change to the scope required.
Timing issues	Action for Pulmonary Fibrosis	This is urgent. APF estimates that there are approximately 10,000 diagnosed IPF patients with FVC >80% in England. Nintedanib slows progression of the disease and increases life expectancy. Since their average life expectancy post-diagnosis is 3-4 years, it is important they are given access to nintedabib as soon as possible. Moreover, many patients are currently prescribed the drug late (FVC less than 80%) because of the serious shortage of pulmonary function tests (PFTs) in hospitals and long waiting lists for hospital appointments due to Covid-19.	Comment noted. No change to the scope required.
	Boehringer Ingelheim	IPF is a devastating disease, which results in substantial disability through deterioration of lung function, physical capability and quality of life and ultimately results in death.(1,2) Decline in FVC appears to be almost linear, with patients with higher FVC at baseline experiencing the same rate of decline in FVC as those with lower FVC values.(3) Furthermore, a recent real-world study of UK patients with IPF has shown that patients treated with antifibrotic therapy had higher median survival than untreated patients, despite the fact that untreated patients had a higher baseline FVC.(4) The goal of treatment is therefore to reduce the rate of FVC decline, as once disease progression has occurred the reduction in lung function and associated symptoms are irreversible.(5) UK clinical experts and patient groups do not support the existing threshold for treatment in NICE guidance, as it results in a delay in access for patients while their FVC declines to 80% predicted; 55% of patients are not prescribed	Comment noted. No change to the scope required.

Section	Stakeholder	Comments [sic]	Action
		antifibrotic treatments at presentation in the UK, the majority of which (63%) is based on patients having an FVC out of the range recommended for treatment by NICE.(6) It is also important to note that even in those individuals who do demonstrate a slower rate of progression prior to initiation of antifibrotic therapy, this initial slower decline does not indicate a lower capacity for treatment effect, or improved survival. A recent study by Aono et al showed that a difference in decline in FVC prior to initiation of an antifibrotic is not associated with a different response to therapy, whereas FVC decline after initiation is strongly associated with mortality risk perhaps rendering the 'watch & wait' approach unreliable.(7) This coupled with delay to diagnosis from onset of symptoms (40% of patients waiting >2 years as per the 2021 BTS registry report), and that nearly half of all IPF patients experience a decline in FVC in the 6 months following diagnosis means patients could have experienced significant lung function loss before even reaching the current 80% threshold or being offered pharmacological therapy.(6,8) As noted above, real-world evidence in UK patients has shown that patients treated with antifibrotics have improved survival compared with untreated patients, despite untreated patients having a higher baseline FVC.(4) Therefore, it does not make sense to delay treatment based on patients' FVC at presentation. In England and Wales, the current management options for patients with IPF who have a FVC >80% predicted are limited to best supportive care and pulmonary rehabilitation. No licensed treatments are available that can reduce disease progression, unlike for patients with an FVC between 50 and 80% predicted where nintedanib and pirfenidone are recommended. However, nintedanib has a consistent treatment effect in patients with FVC above and below 80% predicted, as shown in a subgroup analysis of the INPULSIS trials.(9)	

Section	Stakeholder	Comments [sic]	Action
		According to the 2021 Annual Report from the British Thoracic Society (BTS) ILD Registry, around 38% of people with IPF present with an FVC >80% predicted in the UK.(6) Furthermore, FVC % predicted values have been found to be significantly higher in patients with IPF who have comorbid emphysema, despite their DLCO values being significantly more impaired, indicating more severe disease not captured in the FVC % predicted value alone.(10,11) Patients with comorbid emphysema are a considerable subgroup within the IPF population, comprising up to 35% of all patients.(12) Patients who are taller or physically active will also have an FVC of more than 100% predicted before their lung function begins to decline, and thus could have suffered significant loss of lung volume with significant fibrosis and impaired DLCO but still have FVC >80% predicted.(5) The restriction to patients with an FVC of 50-80% predicted therefore excludes a considerable proportion of patients who could benefit from treatment with nintedanib. Patients with FVC >80% predicted have been unable to access treatment with proven efficacy in IPF for the last 6 years – therefore there is a real unmet need and urgency for this topic to be reviewed.	
	British Thoracic Society	Urgent unmet need as patients with IPF who have an FVC above 80% currently have no available therapy in England apart from supportive care. This is contrary to the marketing authorisation and England is an outlier regarding access to treatment in this cohort of patients, compared to its European counterparts.	Comment noted. No change to the scope required.

Section	Stakeholder	Comments [sic]	Action
Additional comments on the draft remit	British Thoracic Society	The issue is very important for IPF patients as there is option of treating patients with Progressive Fibrosing ILDs with Nintedanib (irrespective of FVC value) but IPF (which is a progressive disease with dismal prognosis) patients are not able to access Anti-fibrotics (either Nintedanib or Pirfenidone) in the UK if the FVC is above 80% predicted. Hence it is utmost important to revise the NICE guidance as the clinical trials had patients with FVC of >80% predicted and there is real world data on its benefit in patients above FVC of 80% threshold.	Comment noted. No change to the scope required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Action for Pulmonary Fibrosis	We suggest you add the word 'disability' into the last sentence of paragraph 1: ….reduced quality of life, disability and death.	Comment noted. The background section of the scope has been amended.
	Boehringer Ingelheim	The background information states, "stakeholders have indicated that only recommending the use of these treatments to when a person has a forced vital capacity (FVC) between 50 and 80% predicted does not reflect current clinical practice". This is not aligned with what we have heard from clinical experts or patient groups, or with what is reported in the BTS ILD Registry Annual Report. These sources all agree that patients with FVC >80% predicted are not currently receiving treatment with nintedanib or pirfenidone due to the recommendations in TA379 and TA504. This is enforced at NHS Trust level by the Blueteq prescribing system. Rather, clinical experts and patient groups	Comment noted. The background section of the scope has been amended.

Section	Consultee/ Commentator	Comments [sic]	Action
		have told us that they do not believe this restriction is appropriate and that they do not support it. Therefore, we request that this statement is changed to read "Stakeholders have indicated that only recommending the use of these treatments to when a person has a forced vital capacity (FVC) between 50% and 80% predicted is inappropriate and not supported by clinical evidence, and that there may be new information to warrant an update of the guidance."	
	British Thoracic Society	The study by Kohr et al provides the most accurate review of survival and lung function decline in IPF patients and provides the background for this appraisal.	Comment noted. No change to the scope required.
Population	Boehringer Ingelheim	As noted above, we would like to explore the possibility of including patients with FVC <50% predicted in the population if it would be possible to withdraw the application for reimbursement in this population if it becomes clear during the appraisal that the recommendation in this group will be negative. If the above is possible, we would like to suggest the population be amended to "adults with idiopathic pulmonary fibrosis with a forced vital capacity above 80% or below 50% predicted". If it is not possible, we suggest the following small change to "adults with idiopathic pulmonary fibrosis with a forced vital capacity above 80% predicted".	Comment noted. TA379 final guidance outlines that drug treatment might not be appropriate for people with a percent predicted FVC of less than 50%. The committee concluded that in clinical practice nintedanib would be appropriate for treating people with a percent predicted FVC of more than 50%. The title and remit of the scope have been updated to

Section	Consultee/ Commentator	Comments [sic]	Action
			nintedanib for treating idiopathic pulmonary fibrosis in people with a forced vital capacity above 80% predicted.
Comparators	Boehringer Ingelheim	We believe that “established clinical management without nintedanib” is an appropriate comparator. According to NICE clinical guideline CG163 this consists of best supportive care, including information and support, symptom relief, management of comorbidities, withdrawal of therapies suspected to be ineffective or causing harm and end of life care. Pirfenidone is not recommended for patients with FVC >80% predicted or <50% predicted, and is therefore not an appropriate comparator.	Comment noted. No change to the scope required.
	British Thoracic Society	Comparator is best supportive care	Comment noted. No change to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
Outcomes	Action for Pulmonary Fibrosis	Yes but we question whether 'progression-free survival' should be considered as an outcome indicator. IPF is a progressive and incurable disease and nintedanib has been shown to slow progression but not to eliminate it.	Comment noted. Progression-free survival has been removed as an outcome.
	Boehringer Ingelheim	Progression-free survival was not included as an outcome in the INPULSIS or TOMORROW trials. It is also not an appropriate endpoint for IPF, given the progressive nature of the disease. Therefore, we do not expect to include evidence on this outcome in our submission and request that it is removed from the scope. We will present evidence on the remaining outcomes (pulmonary function parameters, physical function, exacerbation rate, mortality, adverse effects of treatment and health-related quality of life).	Comment noted. Progression-free survival has been removed as an outcome.
	British Thoracic Society	Health care utilisation and hospitalisations is not considered as an outcome measure	Comment noted. The outcomes listed in the scope are not exhaustive. Healthcare utilisation and hospitalisations will be captured within adverse effects of treatment and health-related quality of life measures.

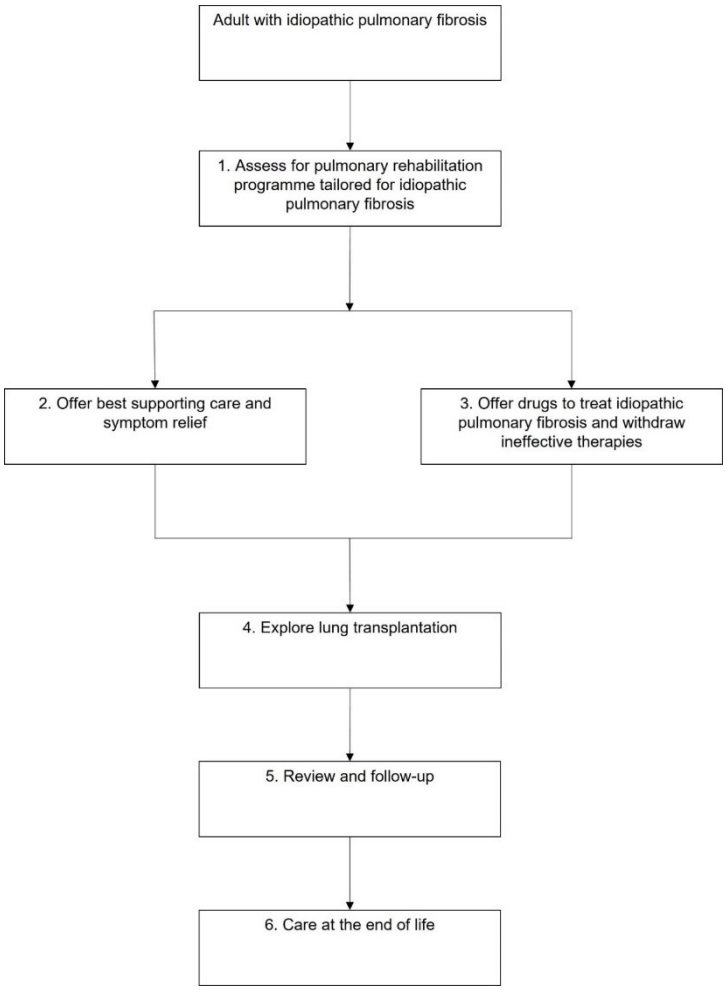
Section	Consultee/ Commentator	Comments [sic]	Action
Economic analysis	British Thoracic Society	Time horizon should be sufficiently long: This will be limited by the published studies as clinical trials only provide data for one year. Post hoc data is now available but NICE should also use registry data and real world studies to look at longer term data especially the BTS and Australian registry data especially when looking at survival, health care utilisation with/without antifibrotic therapy. It is not mentioned how long the time scale for estimating cost effectiveness and clinical benefit would be. I suspect we are looking at least a period of 12-24 months to establish the benefit as decline is disease progression is likely to be over months to years.	Comment noted. No change to the scope required.
Equality	British Thoracic Society	The current NICE approval of pirfenidone and nintedanib in IPF patients with FVC 50-80% provides an inequality of access to life prolonging therapy for patients with FVC above 80%. This depends on the outcome of this review. A negative results will result in an inequality of access to treatment for patients above FVC 80% in IPF as nintedanib is currently available for other progressive fibrotic diseases.	Comment noted. No change to the scope required.
Other considerations	Action for Pulmonary Fibrosis	Anxiety and stress caused to patients with FVC>80% because they are denied access to nintedabib. IPF patients are told on diagnosis they have, on average, only 3-4 years to live and that antifibrotic drugs, which can slow progression and extend life,	Comment noted. No change to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		are only available once their lung function (FVC) deteriorates to 80% of expected. Since many patients remain with an FVC over 80% for 1 to 2 years, the lack of access to treatment is a cause of great anxiety and stress. This anxiety is exacerbated by a strong sense of injustice since (i) patients with non-IPF pulmonary fibrosis can now receive nintedanib on diagnosis and (ii) the UK is the only country in the western world, which does not make nintedanib available on diagnosis.	
	British Thoracic Society	Will have a significant impact on IPF patients who have an FVC above 80% and provide life prolonging therapy – which is not available at present to this patient group who have severe disease Yes this technology can potentially result in a substantial clinical benefit for patients with FVC of >80% and may not fit in QALY calculations. There is evidence from subgroup analyses from pooled data from INPULSIS trials that patients with IPF irrespective of FVC % of <80% or >80% predicted gain similar benefit from the drug in terms of lung function decline (ERJ 2015 46 OA4499; DOI 10.1183/13993003.congress-2015.OA4499	Comment noted. No change to the scope required.
Innovation	Action for Pulmonary Fibrosis	Nintedanib would be innovative and a step change in the management of IPF for patients with FVC>80%, who are currently denied access to the drug. On other health-related benefits see response to last question.	Comment noted. No change to the scope required.
	Boehringer Ingelheim	There are currently no licensed treatments recommended for use in patients with IPF who have FVC >80% predicted, and current management is limited to best supportive care. Nintedanib has shown consistent clinical evidence of slowing disease progression in patients across a spectrum of interstitial lung diseases.(13,14) It has also been shown to have a similar treatment effect in	Comment noted. No change to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		patients with FVC >80% predicted to that seen in patients with FVC <80% predicted.(9) In addition to this, there is evidence that nintedanib treatment is associated with long-term survival benefit in patients with IPF, compared with those who do not receive antifibrotic therapy, as reported in registries of IPF patients across the world.(15–17) As such, nintedanib represents a step-change in treatment for patients with IPF and FVC >80% predicted, providing a much-needed treatment option where there is currently no recommended or reimbursed treatments.	
Questions for consultation	Boehringer Ingelheim	**Which treatments are considered to be established clinical management in the NHS for idiopathic pulmonary fibrosis with a forced vital capacity above 80%?** As stated above, NICE clinical guideline CG163 describes established clinical management for patients with FVC >80% predicted as consisting of best supportive care, including information and support, symptom relief, management of comorbidities, withdrawal of therapies suspected to be ineffective or causing harm and end of life care. **Is pirfenidone considered to be established clinical management in the NHS for idiopathic pulmonary fibrosis with a forced vital capacity above 80%?** Pirfenidone is not recommended by NICE for patients with FVC >80% predicted (use is restricted to patients with an FVC between 50 and 80% predicted in TA504). This is enforced at NHS Trust Level by the Blueteq prescribing system. The committee for TA379 also concluded that pirfenidone was not an appropriate comparator for patients with FVC >80% predicted or <50% predicted.	Comment noted. No change to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Therefore, pirfenidone should not be considered to be established clinical management in the NHS for patients with IPF and FVC >80% or <50% predicted, and is not an appropriate comparator for this appraisal. **Where do you consider nintedanib will fit into the existing care pathway for idiopathic pulmonary fibrosis?** The existing care pathway for IPF patients is described in CG163 (represented in Figure 1 below). We anticipate that nintedanib would be used in part 3 (offer drugs to treat idiopathic pulmonary fibrosis and withdraw ineffective therapies). The proposed change would allow initiation of nintedanib from the point of diagnosis, or when deemed appropriate by the treating physician, without having to wait for further progression until FVC declines to 80% predicted.	

Figure 1: Current clinical pathway of care for idiopathic pulmonary fibrosis (February 2022)



Section	Consultee/ Commentator	Comments [sic]	Action
		Would nintedanib be a candidate for managed access? We do not expect that nintedanib would be an appropriate candidate for managed access. **Do you consider nintedanib to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** See row above. **Do you consider that the use of nintedanib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** **Please identify the nature of the data which you understand to be available to ensure the committee take account of these benefits.** Use of nintedanib as soon as it is deemed appropriate by the treating physicians is highly important for patients, and interviews with patients living with IPF describe the psychological trauma of receiving a diagnosis of IPF and finding out initial information about its prognosis. Many patients experience shock, anxiety and depression-like symptoms following diagnosis.(18,19) These are increased if patients have to wait for their condition to deteriorate before receiving treatment. These concerns are difficult to quantify and include in the QALY calculation.	

Section	Consultee/ Commentator	Comments [sic]	Action
	British Thoracic Society	There are no specific established treatments for IPF patients with FVC >80% and that includes Nintedanib and Pirfenidone. Nintedanib is one of the first line therapeutic intervention in IPF and if approved with FVC>80% predicted patients, it would be a standard of care at the diagnosis of IPF and it would be a candidate for managed access.	Comment noted. No change to the scope required.
Additional comments on the draft scope	Action for Pulmonary Fibrosis	The IPF community (patients, their families and health care workers) has been asking NICE to carry out this appraisal for over 5 years. We hope very much that NICE will expedite the appraisal process and complete it in well under the usual 50 weeks. Every month of delay reduces the life expectancy of approximately 500 newly diagnosed patients each month, who will be denied access to nintedanib.	Comment noted. No change to the scope required.
	British Thoracic Society	It would be absolutely crucial to appraise this guidance on Nintedanib for IPF and we hope that NICE would consider Pirfenidone on similar lines in the near future	Comment noted. No change to the scope required.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope