National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Pirfenidone for treating idiopathic pulmonary fibrosis (review of TA282)

Response to consultee and commentator comments on the draft remit and draft scope

Please note: The following document contains the responses to consultee and commentator comments from draft scope consultations held in July and October 2015.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pirfenidone for treating idiopathic pulmonary fibrosis (review of TA282)

Response to consultee and commentator comments on the draft scope

Section	Consultees	Comments	Action
Background information	British Thoracic Society	The statements are rather weak and do not emphasise the survival advantage of pirfenidone reported in the ASCEND study: this should be a significant driver for maintaining availability of pirfenidone (especially in view of recent data on efficacy of nintedanib).	Comments noted. The background section of the scope is meant to provide a brief overview of the condition and treatment pathway. Details about the results of the ASCEND study will be considered in detail during the appraisal. No changes to the scope are required.
	United Kingdom Clinical Pharmacy Association (UKCPA) Respiratory Group	The median survival is stated as 3 years from diagnosis. However, the clinical course of IPF is variable and consequently this median survival does not reflect the variability seen in subgroups where both slowly progressive and rapidly progressive patient types are recognised. For patients staged using GAP severity assessment survival at 3 years is >80% for Stage I, >50% for Stage II and <25% for Stage III. Patients classified as mild-moderate IPF will generally have a median survival in excess of 3 years.	Comment noted. The background section has been updated to reflect the heterogeneity of the median survival rates for people with IPF.
		In the statement regarding classifying disease severity, the scope states that it is widely accepted that severe IPF is defined as FVC <50% and diffusing capacity <35%, therefore mild-to-moderate IPF can be defined as FVC greater than 50%. However this neglects to use diffusing capacity as a marker of severity, and consequently this should be clarified as mild-to-moderate IPF defined as FVC greater	Comment noted. The background section has been updated to include the diffusing capacity of people who have mild-to-moderate

Section	Consultees	Comments	Action
		than 50% or diffusing capacity >35%. Putting this in to context; the ASCEND study included ~20% patients with DLCO between 30 - 35%	IPF.
The technology/ intervention	British Thoracic Society	p2, end of 1st para ' Committee had some reservations about the lack of an upper limit of per cent predicted FVC'. Not sure what this means - NICE have put an upper limit of 80% on prescription of pirfenidone. This is based on ICER calculations, rather than on data. As an expert community we do not agree on the artificial limits - the licence for pirfenidone is for “mild-moderate IPF” (with no FVC parameter stated), and the trial data included patients with FVC up to 90%. As an expert community we believe that pirfenidone's effect is to slow decline and reduce mortality; therefore current constraints prevent treating potentially the most relevant population i.e. to keep people well rather than to treat once disease is established and progressive. This has been raised in a previous response to NICE, and is important to re-state it here. We feel it is also important to raise the issue of the stopping rule – particularly, as when nintedanib is available, the same arbitrary caveats may not apply which would disadvantage pirfenidone.	Comments noted. The scope for an appraisal frames the decision problem to be addressed in the appraisal. The appraisal committee will consider evidence presented in submissions, including new data from the ASCEND study which included people with a predicted FVC greater than 80%. The statement “Committee had some reservations about the lack of an upper limit of per cent predicted FVC” has been removed from the scope; it was an excerpt from the NICE technology appraisal of pirfenidone for treating idiopathic pulmonary fibrosis, section 4.5. No other changes to the scope are required.

Section	Consultees	Comments	Action
Population	British Thoracic Society	Subgroups to be considered: mention should be made of patients with preserved FVC but falling DLco (often in context of mild emphysema and “baseline” supra-normal FVC) - these patients often have progressive IPF with significant fall in DLco but are denied pirfenidone. In many cases they die before with an FVC>80% If there is a need to create FVC limits, then this subgroup should include only those where fibrosis>emphysema (criteria used in drug trials); those with emphysema and a supra-normal FVC need to be assessed differently.	Comment noted. The draft scope has been updated to include a subgroup analysis by disease severity (defined by FVC and/or diffusing capacity for carbon monoxide) if evidence allows.
	United Kingdom Clinical Pharmacy Association (UKCPA) Respiratory Group	This should specify that diagnosis of IPF is made by a multidisciplinary team (as per CG163)	Comment noted. The scope for an appraisal frames the decision problem to be addressed in the appraisal. No changes to the scope are required.
Comparators	British Thoracic Society	Nintedanib cannot be included as a comparator as it is not NICE approved/we don't know full costs and therefore ICER etc.	Comment noted. The appropriate comparators for pirfenidone are: • best supportive care • nintedanib (subject to ongoing NICE appraisal, only for people with a percent predicted FVC of 50–80%). The scope has been updated to make it

Section	Consultees	Comments	Action
			clear that the comparators are subject to the ongoing NICE appraisal of nintedanib (publication expected January 2016).
	Roche Products Limited	We agree that best supportive care is the correct and only comparator for the appraisal.	Comment noted. The appropriate comparators for pirfenidone are: • best supportive care • nintedanib (subject to ongoing NICE appraisal, only for people with a percent predicted FVC of 50–80%). The scope has been updated to make it clear that the comparators are subject to the ongoing NICE appraisal of nintedanib (publication expected January 2016).
	United Kingdom Clinical Pharmacy Association (UKCPA) Respiratory Group	Pending NICE decision on nintedanib this agent would be an appropriate comparator (disease modifying therapy in use in IPF)	Comment noted. The appropriate comparators for pirfenidone are:

Section	Consultees	Comments	Action
			• best supportive care • nintedanib (subject to ongoing NICE appraisal, only for people with a percent predicted FVC of 50–80%). The scope has been updated to make it clear that the comparators are subject to the ongoing NICE appraisal of nintedanib (publication expected January 2016).
Equality	British Thoracic Society	No equality issues	Comment noted.
	United Kingdom Clinical Pharmacy Association (UKCPA) Respiratory Group	No concerns	Comment noted.
	United Kingdom Clinical Pharmacy Association (UKCPA) Respiratory Group	The use of a stopping criteria (FVC decline >10% over 12 months) may deny treatment to patients who may derive a morbidity/mortality benefit as there is no information to indicate that these benefits are limited to patients whose lung function declines at a slower rate	Comment noted. No change required to scope.
Innovation	British Thoracic Society	Is pirfenidone innovative/impact on health related benefits?- Yes, pirfenidone is the only drug to show a survival advantage - therefore highly important, this seems to be omitted completely from this scope (ASCEND data)	Comment noted. The innovation of a treatment is considered by the appraisal committee based on information presented

Section	Consultees	Comments	Action
			by the company and consultees. No changes to the scope are required.
	Roche Products Limited	Pirfenidone was the first treatment licensed for the management of IPF. As such, it represented a significant step change in the management of the disease at time of regulatory approval. Following the original NICE appraisal (TA282), the ASCEND study has been published. The trial demonstrated pirfenidone to be the first and only treatment to significantly improve survival for patients with IPF. Based on these landmark findings, we consider pirfenidone to continue to be innovative treatment, with significant impact of patients' lives.	Comments noted. The innovation of a treatment is considered by the appraisal committee based on information presented by the company and consultees. No changes to the scope are required.
	United Kingdom Clinical Pharmacy Association (UKCPA) Respiratory Group	Pirfenidone represents a step-change/innovation in the management of patients with IPF. Amelioration of lung function decline may reduce the incidence and severity of IPF related morbidity (breathlessness, cough, pulmonary hypertension, etc) and associated burden of disease, although there is limited information in trial outcomes on which to base calculations. Pirfenidone may also reduce associated healthcare utilisation (e.g. oxygen commencement) and rates of hospitalisation due to IPF (which occur more frequently with increasing disease severity, although these outcomes were not included as trial outcomes).	Comments noted. The innovation of a treatment is considered by the appraisal committee based on information presented by the company and consultees. No changes to the scope are required.

Section	Consultees	Comments	Action
Questions for consultation	Roche Products Limited	We do not consider nintedanib to be a relevant comparator for this appraisal. As it does not represent a current standard of care, it should not be included within the scope of the appraisal.	Comments noted. The appropriate comparators for pirfenidone are: • best supportive care • nintedanib (subject to ongoing NICE appraisal, only for people with a percent predicted FVC of 50–80%). The scope has been updated to make it clear that the comparators are subject to the ongoing NICE appraisal of nintedanib (publication expected January 2016).
	United Kingdom Clinical Pharmacy Association (UKCPA) Respiratory Group	No published information on subgroups (by disease severity) but if available may be appropriate to evaluate separately.	Comment noted. The draft scope has been updated to include subgroup analysis by disease severity (defined by FVC and/or diffusing capacity for carbon monoxide) if evidence allows.

The Royal College of Physicians endorsed the comments made by the British Thoracic Society.

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

The Royal College of Pathologists
Department of Health

National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Pirfenidone for treating idiopathic pulmonary fibrosis (review of TA282)

Response to consultee and commentator 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 scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Action for Pulmonary Fibrosis	Change in FVC over time is the best intermediate outcome related to mortality. Evaluated staging systems include the GAP index (Ley Ann Int Med 2012; 156:684), which includes age and gender as predictors of mortality as expected, but also importantly incorporates DLCO % predicted as the most important single physiological variable. The composite physiology index adds FEV1 to FVC and DLCO (Wells. Am J Respir Crit Care Med 2003; 167:962-9), again the DLCO is the single best physiological variable disease severity as assessed by CT or mortality. Therefore, incorporating DLCO into NICE evaluations may be of benefit over and above relying purely on FVC % predicted. There is no agreed staging system for IPF. These comments about patients with severe disease are reasonable, certainly DLCO<35% at presentation is best predictor of poor outcome so would suggest more severe disease.	Comments noted. The background section of the scope is meant to provide a brief overview of the condition and treatment pathway. The clinical management of a condition will be discussed by the appraisal committee during the appraisal. No changes to the scope are required.
	British Thoracic Society	This is generally correct. We have 2 comments: 1. We disagree with the statement “Treatment with pirfenidone should be	Comments noted. The background section of the scope is meant to

Section	Consultee/ Commentator	Comments [sic]	Action
		discontinued if there is evidence of disease progression (a decline in per cent predicted FVC of 10% or more within any 12 month period)." This statement is not backed up by any specific evidence base. We have commented on this previously. 2. Severe disease defined as (in addition to FVC) as a DLco <35% does not reflect the clinical practice: a value of < DLco <30% should be used practice.	provide a brief overview of the condition and treatment pathway, including a summary of current NICE guidance; for example, the recommendation to discontinue treatment if there is evidence of disease progression. The 10% value was based on expert advice about discontinuing treatment in clinical practice, during the evaluation of pirfenidone. The recommendations in NICE technology appraisal 282 will be considered as part of the planned review. No changes to the scope are required.
	Royal College of Nursing	The statement that there are no formal criteria for defining disease severity is a little ambiguous, depending on what is meant by formal. There is good evidence for the lack of utility of the forced vital capacity (FVC) % predicted at baseline as a predictor of severity, although change in FVC over time is the best intermediate outcome related to mortality. Evaluated	Comments noted. The scope background has been updated: the reference to 'formal criteria' has been

Section	Consultee/ Commentator	Comments [sic]	Action
		staging systems include the GAP index (Ley Ann Int Med 2012;156:684), which includes age and gender as predictors of mortality as expected, but also importantly incorporates diffusing capacity of the lung for carbon monoxide (DLCO) % predicted as the most important single physiological variable. The composite physiology index adds FEV1 to FVC and DLCO (Wells. Am J Respir Crit Care Med. 2003;167:962-9), again the DLCO is the single best physiological variable disease severity as assessed by CT or mortality.	removed. The background section of the scope is meant to provide a brief overview of the condition and treatment pathway. The clinical management of a condition will be discussed by the appraisal committee during the appraisal.
The technology/ intervention	Action for Pulmonary Fibrosis	Yes	Comments noted. No changes to the scope are required.
	British Thoracic Society	Yes	Comments noted. No changes to the scope are required.
	Royal College of Nursing	Yes	Comments noted. No changes to the scope are required.
Population	Action for Pulmonary Fibrosis	Yes Groups to be considered separately are those with an FVC >80% predicted and a DLCO < say 65% predicted	Comments noted. If evidence allows, subgroup analysis by disease severity will be considered. No changes to the scope

Section	Consultee/ Commentator	Comments [sic]	Action
			are required.
	British Thoracic Society	Yes. It's important to know if patients with an FVC >80% benefit from pirfenidone. Data from our ILD registry has shown that of 508 patients with IPF (thus far included in the registry), 39% have an FVC > 80%. This is clearly a large proportion of patients with IPF and we strongly believe it's important to ensure that this cohort of patients is not disadvantaged in any way.	Comments noted. The appraisal committee will consider evidence presented in submissions, including new data from the ASCEND study which included people with a predicted FVC greater than 80%. If evidence allows, subgroup analysis by disease severity will be considered. No changes to the scope are required.
	Royal College of Nursing	Yes Groups to be considered separately are those with a FVC >80% predicted this group miss out.	Comments noted. If evidence allows, subgroup analysis by disease severity will be considered. No changes to the scope are required.
Comparators	Action for Pulmonary Fibrosis	Yes	Comments noted. No changes to the scope are required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Boehringer Ingelheim	Pirfenidone's comparators in this assessment should be consistent with NICE's previous and ongoing assessment for nintedanib for IPF patients (ID752) and defined by the clinical subgroups. Based on the ACD (clauses 4.10, 4.15 and 4.16) for ID752 (dated 11 September 2015; pending FAD, as of the date of this comment submission, 04 November 2015), the appropriate comparator for nintedanib was considered by the committee to be: • pirfenidone for patients with percent predicted FVC of 50% to 80%, and • best supportive care for patients with percent predicted FVC of more than 80%.	Comments noted. The appropriate comparators for pirfenidone are: • best supportive care • nintedanib (subject to ongoing NICE appraisal, only for people with a percent predicted FVC of 50–80%). The scope has been updated to make it clear that the comparators are subject to the ongoing NICE appraisal of nintedanib (publication expected January 2016).
	British Thoracic Society	Nintedanib is not currently licensed in the UK, so we are somewhat surprised that it is being used as a comparator at this point.	Comments noted. Nintedanib has a marketing authorisation in the UK "in adults for the treatment of Idiopathic Pulmonary Fibrosis (IPF)." No changes to the scope

Section	Consultee/ Commentator	Comments [sic]	Action
			are required.
	Roche	We note the most significant change in this revised draft scope is the addition of nintedanib as a comparator. This is justified by NICE on the basis that – since the last scoping consultation in April – nintedanib has now received Marketing Authorisation, and final NICE guidance is anticipated in the short-term. NICE have not yet produced final guidance on the use of nintedanib in the treatment of IPF. Assuming the final recommendation is no more restrictive than described in September's ACD, there still remains uncertainty in the population in which nintedanib is recommended, along with any discontinuation rules. The next stage of the appraisal process (ACD or FAD) is not yet confirmed by NICE, nor the likely time frame. We are currently working towards making a submission to NICE in January. The addition of nintedanib represents a major change to the appraisal scope, and the on-going uncertainty in the comparison which will be required generates significant further difficulty in the preparation of a high-quality and timely dossier. In the context of an HTA, relevant comparators to the technology under review are generally considered to be those which are likely to be displaced, should the new technology be adopted. As nintedanib is still under-going assessment by NICE, and use in England and Wales remains limited at this time in comparison to pirfenidone, it is unclear how nintedanib can be considered to be a relevant comparator to pirfenidone.	Comments noted. Preliminary NICE guidance recommends nintedanib as an option for treating idiopathic pulmonary fibrosis, only if: • the person has a forced vital capacity (FVC) between 50% and 80% of predicted • the company provides nintedanib with the discount agreed in the patient access scheme and • treatment is stopped if disease progresses (a confirmed decline in percent predicted FVC of 10% or more) in any 12-month period. Clinical commissioning

Section	Consultee/ Commentator	Comments [sic]	Action
			groups, NHS England and local authorities are required to comply with the recommendations in NICE technology appraisals within 3 months of its date of publication. If final guidance, expected in January 2016, remains unchanged it is expected that at the time NICE publishes preliminary guidance for pirfenidone, nintedanib will be part of clinical practice for treating idiopathic pulmonary fibrosis. No changes to the scope are required.
	Royal College of Nursing	Yes	Comments noted. No changes to the scope are required.
Outcomes	Action for Pulmonary Fibrosis	Yes	Comments noted. No changes to the scope are required.
	British Thoracic	Yes	Comments noted. No

Section	Consultee/ Commentator	Comments [sic]	Action
	Society		changes to the scope are required.
	Royal College of Nursing	Yes	Comments noted. No changes to the scope are required.
Economic analysis	Action for Pulmonary Fibrosis	Should be based on a severity model which incorporates DLCO as well as FVC rather than FVC alone. Ideally should use quality of life data but this is limited.	Comments noted. The company is responsible for developing and presenting an economic analysis for a consideration by the appraisal committee. No changes to the scope are required.
	British Thoracic Society	We sincerely hope that the calculated QALY takes account of the fact that pirfenidone has been shown to prolong life	Comments noted. A quality-adjusted life year (QALY) takes into account both the quantity and quality of life generated by healthcare interventions. The number of QALYs produced by a treatment is considered by the appraisal committee based on

Section	Consultee/ Commentator	Comments [sic]	Action
			information presented by the company and the critique provided by the Evidence Review Group. No changes to the scope are required.
	Royal College of Nursing	Should be based on a severity model which incorporates DLCO as well as FVC rather than FVC alone	Comments noted. The company is responsible for developing and presenting an economic analysis for a consideration by the appraisal committee. No changes to the scope are required.
Equality and Diversity	Action for Pulmonary Fibrosis	The use of FVC alone to assess severity and for use in the cost-effective model is discriminatory. Some patients die of their IPF when their FVC remains above 80% predicted. Some of these patients have coexisting emphysema (which might also be due to traction from the lung fibrosis), and some do not have any emphysema as assessed on CT. Patients with FVC>80% can have clinically significant fibrosis - limitations of current lung function measurements, and FVC can be preserved or maintained due to co-existing emphysema. They should be considered for treatment if there are progressive symptoms, declining lung function and/or radiographic evidence of progressive fibrosis. The use of ECCS predicted lung function tables also discriminates against some ethnic minorities, particularly those from south Asia where predicted equations for lung function are not adequately developed. Similarly it	Comments noted. All comments about equality and diversity will be presented to the appraisal committee for consideration when making their recommendations. NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good

Section	Consultee/ Commentator	Comments [sic]	Action
		discriminates against the older populations as it is derived from populations under the age of 70, whereas the average age of patients with IPF is 72. There is considerable variation in the algorithms that are used to extrapolate the % predicted FVC which again discriminates against older patients with IPF. Similarly, height measurements (crucial for determining % FVC) are less accurate in the elderly or patients with disability due to difficulty standing straight, again leading to considerable discrimination against the elderly or disabled if using % predicted FVC for the prescription of high cost drugs. In clinical practice there are people who have no impairment of physical function whose lung volumes are <60% of the ECCS predicted values. The patients with IPF and FVC <45% who are alive are those from ethnic minorities where the predicted equations discriminate and who are currently precluded from treatment with pirfenidone.	relations between people with particular protected characteristics and others. No changes to the scope are required.
	Royal College of Nursing	The use of FVC alone to assess severity and for use in the cost-effective model seem unfair. Some patients die of their idiopathic pulmonary fibrosis (IPF) when their FVC remains above 80 % predicted. Some of these patients have coexisting emphysema (which might also be due to traction from the lung fibrosis), and some do not have any emphysema as assessed on CT. Our members have suggested that in clinical practice, the use of European Coal and Steel ECCS predicted lung function tables does not seem to be favourable to all communities in the way it calculates lung volume. The calculation seems to be more favourable to those who are taller and seems less favourable to communities that are predominantly of a smaller frame for example some ethnic minority groups, particularly those from South Asia, where predicted equations for lung function are not adequately established. Our members have indicated that in clinical practice they are aware of some patients who have no impairment of physical function whose lung volumes are <60% of the ECCS predicted values. The only patients with IPF and FVC	Comments noted. All comments about equality and diversity will be presented to the appraisal committee for consideration when making their recommendations. NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected

Section	Consultee/ Commentator	Comments [sic]	Action
		<45% who are alive appear to be those from ethnic minorities where the predicted equations could be skewed because of the measuring tool, and who are currently precluded from treatment with pirfenidone.	characteristics and others. No changes to the scope are required.
Innovation	Action for Pulmonary Fibrosis	Yes	Comment noted. The innovation of a treatment is considered by the appraisal committee based on information presented by the company and consultees. No changes to the scope are required.
	British Thoracic Society	The ASCEND trial demonstrated (pooled data with CAPACITY) that pirfenidone reduces all cause mortality. This was a step change in the understanding of the benefits of pirfenidone. The respiratory community in the UK was attuned to the importance of this; anecdotally, prescriptions for pirfenidone increased dramatically after this publication, highlighting its importance.	Comment noted. The innovation of a treatment is considered by the appraisal committee based on information presented by the company and consultees. No changes to the scope are required.
	Roche	Pirfenidone was the first treatment licensed for the management of IPF. As such, it represented a significant step change in the management of the disease at time of regulatory approval. Following the original NICE appraisal (TA282) the ASCEND study has been	Comment noted. The innovation of a treatment is considered by the appraisal

Section	Consultee/ Commentator	Comments [sic]	Action
		published. The trial demonstrated pirfenidone to be the first and only treatment to significantly improve survival for patients with IPF. Based on these landmark findings, we consider pirfenidone to continue to be innovative treatment, with significant impact of patients' lives.	committee based on information presented by the company and consultees. No changes to the scope are required.
	Royal College of Nursing	Yes	Comment noted. The innovation of a treatment is considered by the appraisal committee based on information presented by the company and consultees. No changes to the scope are required.
Other considerations	Roche	The evidence available to allow subgroup analyses are being assessed, although this may be limited by the availability of data for comparator treatment(s)	Comment noted. No changes to the scope are required.
Additional comments on the draft scope	British Thoracic Society	We strongly suggest that NICE should consider delaying this TA until after publication of the nintedanib TA. We are strongly against an upper cap of FVC of 80%. This cap clearly disadvantages too many patients.	Comments noted. This topic has been scheduled into the NICE work programme. Final guidance on nintedanib is anticipated in January 2016.

Section	Consultee/ Commentator	Comments [sic]	Action
			Comments noted. The appraisal committee will consider evidence presented in submissions, including new data from the ASCEND study which included people with a predicted FVC greater than 80%. No changes to the scope are required.

The Royal College of Physicians endorsed the comments made by the British Thoracic Society.

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

Department of Health
Royal College of Pathologists