National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Nintedanib for treating idiopathic pulmonary fibrosis

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Appropriateness	Action for Pulmonary Fibrosis	Yes	Comment noted. No change to the scope required.
	Boehringer Ingelheim	Appropriate	Comment noted. No change to the scope required.
	British Thoracic Society	Appropriate - addresses areas of unmet need in the treatment of a progressive and serious condition.	Comment noted. No change to the scope required.
Wording	Action for Pulmonary Fibrosis	Yes	Comment noted. No change to the scope required.
	Boehringer Ingelheim	Yes	Comment noted. No change to the scope required.
	British Thoracic	Strengthen prognosis argument - prognosis similar to many cancers. Make it	Comment noted. The

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	Society	clear that until 2013, no treatment available in the UK. Current licenced treatment for IPF has an adverse side effect profile in a significant proportion, and also has limitations placed by NICE on its use in mild and progressive disease (even if rate of progression slowed) - hence urgent need for additional/alternative therapies. On page 1 of draft scope it says 'pirfenidone treatment should be stopped if person's FVC falls by 10%' - should be re-phrased as the NICE guidance states that…pirfenidone should be stopped. The ILD community do not generally agree with this NICE ruling as any progression data look at 6 month decline of 10% (not 12 month) and this issue was not debated significantly before inclusion in the pirfenidone TA. p2. 'Nintedanib is being studied in clinical trials' - should insert reference for NEJM paper May 2014 for published trial.	background section has been revised to reflect the wording used in TA282
Timing Issues	Action for Pulmonary Fibrosis	Very urgent as there is very little alternative treatment. Delay may mean that some patients will have deteriorated thus rendering them ineligible to be prescribed with Nintedanib. There is still a large number of disenfranchised patients where FVC is >80% or <50%.	Comment noted. No change to the scope required.
	British Thoracic Society	Urgent - within a year	Comment noted. No change to the scope required.
Additional comments on the draft remit	Action for Pulmonary Fibrosis	None	Comment noted. No change to the scope required.

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	Boehringer Ingelheim	No further comments	Comment noted. No change to the scope required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	Action for Pulmonary Fibrosis	Complete and accurate	Comment noted. No change to the scope required.
	Boehringer Ingelheim	No comments	Comment noted. No change to the scope required.
	British Thoracic Society	Reasonably general/lay application	Comment noted. No change to the scope required.
	InterMune	1) The penultimate sentence is not accurate. The sentence should read "Treatment with pirfenidone should be discontinued if there is evidence of disease progression (a decline in per cent predicted FVC of 10% or more) within any 12 month period." 2) A recently published trial [Ref 1] concluded that compared with placebo, acetylcysteine offered no benefit with respect to the preservation of FVC in patients with idiopathic pulmonary fibrosis with mild to-moderate impairment in lung function. We believe this information should be included in the	The background section of the scope has been amended. Comment noted. No change to the scope required.

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		'Background Information' section. Ref 1: N Engl J Med 2014; 370:2093-2101May 29, 2014DOI: 10.1056/NEJMoa1401739	
The technology/ intervention	Action for Pulmonary Fibrosis	Yes	Comment noted. No change to the scope required.
	Boehringer Ingelheim	Yes	Comment noted. No change to the scope required.
	British Thoracic Society	Yes	Comment noted. No change to the scope required.
Population	Action for Pulmonary Fibrosis	Yes	Comment noted. No change to the scope required.
	Boehringer Ingelheim	Yes	Comment noted. No change to the scope required.
	British Thoracic Society	Yes. Need to consider mild disease (as currently no treatment available for FVC>80) with aim of prevention of decline, and consider looking at patients previously having acute exacerbations (although practically may be difficult). Diagnosis of IPF - there are areas of uncertainty within this diagnosis reflecting limitations of imaging and classification. Current definition would	Comment noted. Consultees at the scoping workshop considered that the population was defined appropriately. No

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		include "definite" and "probable" IPF	change to the scope required.
	InterMune	The population should reflect the trial population which is patients - • age ≥ 40 years. • FVC ≥ 50% of predicted. • DLCO (corrected for Hb) 30-79% of predicted. Patients with a risk of bleeding or expecting to require anticoagulation should be excluded. Patients with Myocardial Infarct/Unstable Angina in the last 6 months should be excluded.	Comment noted. Consultees at the scoping workshop considered that the population was defined appropriately. No change to the scope required.
Comparators	Action for Pulmonary Fibrosis	Established treatment is pirfenidone	Consultees at the scoping workshop agreed that pirfenidone was an appropriate comparator.
	Boehringer Ingelheim	As described in NICE clinical guideline 163 best supportive care includes all aspects associated with holistic clinical care. The guideline states that this should be provided to all patients at the point of diagnosis with IPF and that this should be tailored to the individual patient's needs. This is therefore not a specific, targeted pharmacological intervention for IPF and as such is not an appropriate comparator for nintedanib. N-acetylcysteine is not licensed for the treatment of IPF. A recently published study (PANTHER-IPF NEJM May 2014) investigating N-acetylcysteine monotherapy in patients with IPF demonstrated no clinical benefit over	Comments noted. N-acetylcysteine has been removed as a comparator based on NICE's guide to the methods of technology appraisal (section 2.2.4): "The scope identifies all potentially relevant comparators,

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		placebo in the maintenance treatment of IPF. As such it does not fulfil the criteria to be described as a disease modifying pharmacological intervention and should not be used as a comparator for nintedanib.	taking into account issues likely to be considered by the Appraisal Committee when selecting the most appropriate comparator" and (section 6.2.1): "Specifically when considering an 'unlicensed' medicine, the Appraisal Committee will have due regard for the extent and quality of evidence, particularly for safety and efficacy, for the unlicensed use."
	British Thoracic Society	Yes - Pirfenidone = best alternative care. Data on NAC mixed after Panther-IPF and not a licenced treatment for IPF. NAC helpful for cough in many cases i.e. symptom control. The efficacy of N-acteylcysteine is not supported by recent study results - it is rarely used as stand-alone treatment	Consultees at the scoping workshop agreed that pirfenidone was an appropriate comparator. N-acetylcysteine has been removed as a comparator from the scope (see above).
	InterMune	A recently published trial [Ref 1] concluded that compared with placebo, acetylcysteine offered no benefit with respect to the preservation of FVC in	N-acetylcysteine has been removed as a

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		patients with idiopathic pulmonary fibrosis with mild to-moderate impairment in lung function. Indeed, during the single technology assessment (STA) of pirfenidone, results of the PANTHER study found triple therapy offered no benefit in the preservation of FVC and showed increased mortalities / hospitalisations. In this instance, the NICE Committee concluded that, although specified in the NICE scope, triple therapy was no longer routine or best practice in the NHS for patients starting treatment for IPF and could no longer be considered a comparator for pirfenidone We therefore suggest that NICE apply a consistent approach in this scope with that taken in the appraisal of pirfenidone. Thus, unlicensed treatments that (based on recently published evidence) do not offer any benefit in the treatment of IPF should not be considered as comparators. Consequently, we believe that acetylcysteine should be removed as a comparator.	comparator from the scope (see above).
Outcomes	Action for Pulmonary Fibrosis	Yes	Comment noted. The Consultees considered that all appropriate outcomes had been included in the scope. No change to the scope required.
	Boehringer Ingelheim	We suggest the addition of the rate of change in lung function parameters to assess the impact of therapy on disease progression. Progression-free survival is a composite end-point that has not been clearly defined in respiratory research.	Comment noted. The Consultees considered that all appropriate outcomes had been included in the scope because change in lung

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			function would be included within pulmonary function parameters. No change to the scope required.
	British Thoracic Society	Yes	Comment noted. No change to the scope required.
	InterMune	Yes	Comment noted. No change to the scope required.
Economic analysis	Action for Pulmonary Fibrosis	Yes	Comment noted. No change to the scope required.
	Boehringer Ingelheim	No comments	Comment noted. No change to the scope required.
	British Thoracic Society	Ideally 1 year	Comment noted.
Equality and Diversity	Action for Pulmonary Fibrosis	No exclusions identified	Comment noted. No change to the scope required.
	Boehringer	No comments	Comment noted. No

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	Ingelheim		change to the scope required.
	British Thoracic Society	No concerns	Comment noted. No change to the scope required.
Innovation	Action for Pulmonary Fibrosis	Yes, possibly as an alternative to Pirfenidone. Phases 1-3 clinical trials data.	Comment noted. No change to the scope required.
	Boehringer Ingelheim	IPF is a devastating condition with a significant need for the development of new therapies. Nintedanib offers a new class of drug for the maintenance treatment of idiopathic pulmonary fibrosis. It is the first pharmacological treatment to offer consistent, positive results from a pair of identical phase III clinical trials including a broad range of IPF patients. It offers convenience to patients with twice daily administration of a single capsule.	Comment noted. No change to the scope required.
	British Thoracic Society	Perhaps make it clear that until 2013, no treatment available in the UK. Current licenced treatment for IPF (pirfenidone) has an adverse side effect profile in a significant proportion, and also has limitations placed by NICE on its use in mild and progressive disease (even if rate of progression slowed) - hence urgent need for additional/alternative therapies. Data - NEJM trial May 2014 The technology is novel in its pharmacological mechanism, and is intended to treat a serious condition with only one licensed alternative therapy (pirfenidone). Pirfenidone has limitations in terms of licensing (FVC 50-80%) which exclude patients with less severe impairment of FVC, or patients with IPF who have concomitant emphysema, which will tend to artificially elevate	Comment noted. No change to the scope required.

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		FVC. There are therefore areas of unmet need within the licensing indication. Published data would support the use of nintedanib in patients with less severe impairment of FVC, who may not currently meet licensed indications for pirfenidone. Whether these patients should be considered as having "mild" disease is debatable, since the study populations had impairment of gas transfer with mean (SD) DLCO of 47 (12)%, which is not a trivial impairment, and the natural history of the disease leads to progressive symptoms, impairment and mortality	
	InterMune	Nintedanib is not a step change in the management of IPF as a recently completed clinical trial for pirfenidone in the same population has demonstrated an improvement in all-cause mortality in addition to IPF related mortality which has not been replicated by this technology.	Comment noted. No change to the scope required.
Other considerations	Action for Pulmonary Fibrosis	None	Comment noted. No change to the scope required.
	Boehringer Ingelheim	No comments	Comment noted. No change to the scope required.
	InterMune	Patients with IPF have a high prevalence of Ischaemic Heart Disease (up to 58%) and an increased risk of vascular disease three times greater than the general population. [Ref 2,3] Patients with IHD should be excluded from consideration for use with nintedanib because they were excluded from the clinical trial protocol. [Ref 4]. Recent NICE guidance (CG180) recommends the use of warfarin and newer oral anticoagulants to reduce the risk of stroke in certain patients with atrial	Consultees at the scoping workshop did not consider that people with IPF who have a high prevalence of ischaemic heart disease or unstable angina would be an appropriate

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		fibrillation (AF) rather than aspirin and we believe these patients should also be excluded from consideration as warfarin is contraindicated with nintedanib. Ref 2: Thorax 2011;66:A61-A62 doi:10.1136/thoraxjnl-2011-201054b.134 Ref 3: Am J Respir Crit Care Med. 2008 Dec 15;178(12):1257-61. doi: 0.1164/rccm.200805-725OC. Ref 4: N Engl J Med 2014; 370:2071-2082May 29, 2014DOI: 10.1056/NEJMoa1402584	subgroup. No change to the scope required.
Questions for consultation	Boehringer Ingelheim	Which treatments are considered to be established clinical practice in the NHS for IPF? Pirfenidone is currently the only licensed therapy for the maintenance treatment of IPF. Other pharmacological agents are used as part of best supportive care to manage symptoms and comorbidities but this is not standardised throughout the NHS. Are there any subgroups of people in whom nintedanib is expected to be more clinically effective and cost effective or other groups that should be examined separately? Nintedanib clinical studies recruited patients with FVC percentage predicted of ≥50%, therefore data does not exist in patients below this threshold. Where do you consider nintedanib will fit in the existing NICE pathway 'idiopathic pulmonary fibrosis'? Nintedanib is a targeted first line therapy indicated to reduce the rate of disease progression and of acute exacerbations in patients with IPF who have an FVC percentage predicted of ≥50%.	Consultees agreed that the list of comparators was appropriate. No change to scope required Consultees agreed there were no subgroups that should be added to the scope. Comment noted. No change to the scope required.
	British Thoracic	Pirfenidone is the only relevant comparator treatment. N-acetylcysteine is rarely used as stand-alone treatment, and published evidence points towards	Comment noted. Consultees agreed that

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	Society	lack of efficacy.	comparators listed in the scope were appropriate. No change to the scope required.
Additional comments on the draft scope	Action for Pulmonary Fibrosis	Long term toxicity of tyrosine-kinase inhibitors.	Comment noted. No change to the scope required.
	Boehringer Ingelheim	No further comments	Comment noted. No change to the scope required.
	British Thoracic Society	"Where will nintedanib fit in existing NICE pathway for IPF?" Nintedanib is likely to be considered in patients with less severe impairment of FVC than pirfenidone, or in patients who have proved intolerant of pirfenidone. Published evidence for nintedanib does not show benefits in terms of mortality and the data on reduction in risk of exacerbation is mixed. By contrast, there is now evidence for pirfenidone having an impact on both mortality and exacerbation risk. This may result in patients being considered for pirfenidone in the event of an episode of exacerbation. There is no data to support co-administration.	Comment noted. No change to the scope required.
	InterMune	InterMune support NICEs intention to appraise this technology through its STA process. There is a high unmet need for patients with IPF who cannot take pirfenidone and therefore nintedanib should be positioned as a 2nd line option for these patients. Consideration should also be given to the benefits of an update to the	Comment noted. No change to the scope required.

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		pirfenidone STA. While there is positive guidance in some patient groups (patients with FVC <80% and those who do not decline by more than 10% in 12 months), new evidence improves the cost effectiveness of pirfenidone in these groups of patients, but also in patients with FVC >80%. InterMune strongly feel that the magnitude of effect on cost effectiveness will allow NICE to expand the group of patients who may access pirfenidone to the full mild to moderate population and will also allow removal of the stopping rule which, on investigation, appears to be less cost effective than no stopping rule at all – patients that decline can also stabilise when remaining on treatment whereas removal of therapy appears to exacerbate decline. Revising the STA also provides the opportunity for NICE to consider an MTA at a later stage.	
	Royal College of Physicians	We wish to fully endorse the comments submitted by the British Thoracic Society.	Comment noted. No change to the scope required.

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

Department of Health
Healthcare Improvement Scotland
The Royal College of Pathologists

Single Technology Appraisal (STA)

Nintedanib for treating idiopathic pulmonary fibrosis [ID752]

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	*Proposal made by:*		*Action taken:* Removed/Added/Not included/Noted	*Justification:*
	Remove British Lung Foundation from patient/carer group consultees.	British Lung Foundation		Removed	Removed at organisation's request as they do not comment on individual drugs.