

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Pirfenidone for treating idiopathic pulmonary fibrosis

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using pirfenidone in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the [committee papers](#)).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
 - NICE especially welcomes comments on the committee's consideration of equality issues, described in section 4.20.

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using pirfenidone in the NHS in England.

For further details, see NICE's [guide to the processes of technology appraisal](#).

The key dates for this appraisal are:

Closing date for comments: 24 June 2016

Second appraisal committee meeting: 6 July 2016

Details of membership of the appraisal committee are given in section 7.

1 Recommendations

1.1 This appraisal considered changes to [technology appraisal guidance 282](#) proposed by the company, specifically:

- expanding the population to include people with a forced vital capacity (FVC) above 80% predicted
- removing the recommendation to stop pirfenidone if the disease progresses
- a different patient access scheme for pirfenidone (a higher price).

No changes to technology appraisal guidance 282 are recommended.

1.2 Pirfenidone continues to be recommended as an option for treating idiopathic pulmonary fibrosis in adults only if:

- the person has an FVC between 50% and 80% predicted
- the company provides pirfenidone with the discount agreed in the patient access scheme for [technology appraisal guidance 282](#).

1.3 Treatment with pirfenidone that is recommended according to 1.2 should be stopped if there is evidence of disease progression (a decline in percent predicted FVC of 10% or more within any 12-month period).

1.4 This guidance is not intended to affect the position of patients whose treatment with pirfenidone was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2 The technology

2.1 Pirfenidone (Esbriet, Roche) is an oral immunosuppressant with anti-inflammatory and antifibrotic effects. Pirfenidone has a marketing

authorisation in the UK for treating mild to moderate idiopathic pulmonary fibrosis in adults.

2.2 The summary of product characteristics states that the very common adverse reactions (affecting 1 in 10 or more people) associated with using pirfenidone are nausea, rash, diarrhoea, fatigue, dyspepsia, anorexia, headache and photosensitivity reaction. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The recommended dosage of pirfenidone is three 267 mg capsules 3 times daily (that is, a total of 2,403 mg per day). The list price of pirfenidone is £501.92 for 63 capsules (excluding VAT; British national formulary online, accessed May 2016). This equates to a daily cost of £71.70. During the original NICE appraisal of pirfenidone ([technology appraisal guidance 282](#)), the company agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of pirfenidone, with the discount applied at the point of purchase or invoice. The company subsequently proposed that the patient access scheme discount for pirfenidone would be reduced (that is, the price would be higher) in light of new clinical data available since technology appraisal guidance 282. The Department of Health agreed that the reduced discount could be taken into account in the present appraisal. The level of both discounts is commercial in confidence. The Department of Health considered that the patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Evidence

The appraisal committee (section 7) considered evidence submitted by Roche Products and a review of this submission by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence.

4 Committee discussion

The appraisal committee reviewed the new data available on the clinical and cost effectiveness of pirfenidone, having considered evidence on the nature of idiopathic pulmonary fibrosis and the value placed on the benefits of pirfenidone by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Review objective

4.1 The committee recognised that this appraisal was a review of [technology appraisal guidance 282](#), and that the company had proposed the following changes to the current guidance:

- To remove the requirement to stop treatment if a person's percent predicted forced vital capacity (FVC) drops by 10% (referred to as 'the stopping rule').
- To provide pirfenidone with a new patient access scheme which has a lower discount and therefore a higher price.
- To expand the current recommendation to include people with an FVC above 80% predicted.

The committee considered each of these items in turn.

Removing the stopping rule

4.2 The committee discussed the stopping rule in NICE guidance on pirfenidone ([technology appraisal guidance 282](#)) and nintedanib ([technology appraisal guidance 379](#)). The committee discussed whether removing the stopping rule would be beneficial for patients, that is, whether there is a benefit of continuing treatment with pirfenidone after a 10% decline in percent predicted FVC. It discussed the company's post-hoc subgroup analysis of outcomes for people who had a decline in percent predicted FVC of 10% or more during the first 6 months of

treatment. This analysis showed that fewer people in the pirfenidone group (1 patient out of 24) experienced a further 10% decline in percent predicted FVC compared with the placebo group (15 patients out of 60; $p=0.032$). The committee considered that there was substantial uncertainty in the results of this analysis for several reasons:

- The sample size of 84 patients was small, meaning that the analysis may not have had enough statistical power to detect differences between the groups.
- The analysis broke the randomisation of the clinical trials.
- To test the hypothesis that people benefit from continuing pirfenidone treatment after disease progression, it would be more informative to compare against people who stopped pirfenidone after disease progression, rather than people who had been randomised to placebo at baseline.

The committee concluded that the company's evidence did not conclusively show that people continue to benefit from pirfenidone after disease progression.

- 4.3 The committee discussed whether the stopping rule was used in clinical practice, and whether it was considered clinically relevant. It heard from the clinical experts that they do follow it. The experts explained that, before stopping treatment, they retest FVC to confirm that the 10% drop is not temporary, which might happen with an infection. The clinical experts did not agree that a 10% drop in predicted FVC means that a treatment is not working, because it is difficult to know how a person's lung function would have deteriorated without treatment. However, the experts could not suggest a better way of defining treatment success. The committee heard that clinical experts want to have the option of continuing treatment after disease progression because, in the experts' experience, such treatment may be beneficial (although this benefit is unproven). The

committee agreed to consider cost-effectiveness analyses both with and without the stopping rule applied.

- 4.4 The committee discussed whether the company's model appropriately incorporated the treatment stopping rule. The evidence review group (ERG) explained that incremental cost-effectiveness ratios (ICERs) including the stopping rule for pirfenidone would likely be biased in favour of pirfenidone when compared with best supportive care because, in the model, the stopping rule reduced pirfenidone costs without affecting treatment outcomes. The committee also noted that scenarios including stopping rules do not reflect the evidence base because the clinical trials did not include stopping rules. The committee concluded that analyses including a stopping rule for pirfenidone would underestimate the ICER because of the model structure.

Cost effectiveness with the new patient access scheme applied

Current practice

- 4.5 The committee discussed how idiopathic pulmonary fibrosis is managed in current NHS practice. The clinical experts explained that they offer treatment with pirfenidone or nintedanib if a person's percent predicted FVC is between 50% and 80% (moderate disease); this reflects the NICE guidance on pirfenidone ([technology appraisal guidance 282](#)) and nintedanib ([technology appraisal guidance 379](#)). The clinical experts noted that people with an FVC above 80% predicted (mild disease) would be offered best supportive care because NICE does not recommend pirfenidone or nintedanib in this population. The committee recalled discussions from the nintedanib appraisal about the limitations of using percent predicted FVC to assess lung function in people with idiopathic pulmonary fibrosis. For example, percent predicted FVC can be less sensitive in people with emphysema and idiopathic pulmonary fibrosis (that is, FVC could be high despite significant pulmonary disease). The committee for this appraisal recognised the limitations of FVC but

understood that in clinical practice the wider patient characteristics would be taken into account in interpreting percent predicted FVC.

- 4.6 The committee discussed whether nintedanib was a relevant comparator. The committee was aware that during the nintedanib appraisal, it concluded that pirfenidone and nintedanib had similar estimates for cost effectiveness, but that neither nintedanib nor pirfenidone was cost effective compared with best supportive care. The committee recognised that nintedanib may not be considered a good use of NHS resources relative to best supportive care. The committee was aware that NICE published its guidance on nintedanib on 27 January 2016 and heard from the clinical experts for the present appraisal that they had had access to nintedanib for only a week. Therefore the committee considered that nintedanib was not embedded in clinical practice. The committee concluded that, when considering the cost effectiveness of pirfenidone, the appropriate comparator was best supportive care. The committee did not consider the comparison with nintedanib further.

New clinical evidence

- 4.7 The committee recognised that the guidance review was triggered because data were now available from the ASCEND trial of pirfenidone, which were not available during NICE [technology appraisal guidance 282](#). The committee was aware that the company had included the ASCEND data in a network meta-analysis with data from 3 other placebo-controlled trials of pirfenidone (CAPACITY 1, CAPACITY 2 and SP3), which were all available for technology appraisal 282. The committee noted that the ERG had amended the company's network meta-analysis:
- The committee understood that the CAPACITY trials had a 72-week follow-up period, and that the trial outcomes were pre-specified to be measured after 72 weeks, but heard that the company used 52-week data in the meta-analysis because the sample size informing the outcomes beyond week 52 was small. The company further explained

that a 52-week analysis of pooled data from the CAPACITY and ASCEND trials was pre-specified in the statistical plan for ASCEND (which had a 52-week follow up), whereas a pooled analysis including 72-week data from the CAPACITY trials was post hoc. The committee nonetheless agreed that it was more appropriate to use the longer term data from the CAPACITY trials (that is, 72 week data) in the network meta-analysis.

- The committee agreed that, when there are differences between studies, it is more appropriate to use the predictive distribution for informing the model (as the ERG had done) instead of the credible interval (used by the company). However, the committee noted that the choice of method would have little effect on the point estimates of the ICER.
- The committee agreed with the ERG's rationale for excluding the SP3 trial; that is, because it evaluated lower doses of pirfenidone (not licensed in the UK), applied different eligibility criteria and reported differences from the other 3 pirfenidone trials in some baseline characteristics. However, the committee recalled that, during its technology appraisal of [nintedanib for treating idiopathic pulmonary fibrosis](#), it had concluded that it was appropriate to include SP3 in the network meta-analysis because the population was not substantially different from the other pirfenidone trials. The committee recognised that expert opinion could argue for or against including the results from SP3. It noted that including SP3 had a minimal impact on the hazard ratios estimated from the network meta-analysis, and it agreed to include SP3 in the analyses to be consistent with the appraisal of nintedanib.

4.8 The committee was aware that the company stated, in its submission, that ASCEND is the first trial to suggest that a treatment for idiopathic pulmonary fibrosis can improve overall survival. The committee noted that the difference between pirfenidone and placebo for all-cause mortality (in

favour of pirfenidone) was not statistically significant if the ASCEND or CAPACITY trials were analysed separately. The committee noted that the survival benefit of pirfenidone was statistically significant only when combining the 52-week all-cause mortality data from the trials:

- hazard ratio 0.49 when CAPACITY 1 and 2 were pooled, $p=0.047$
- hazard ratio 0.52 when ASCEND and the 2 CAPACITY trials were pooled, $p=0.011$
- hazard ratio 0.52 when ASCEND, the 2 CAPACITY trials and SP3 were meta-analysed by the company, 95% credible interval 0.30 to 0.89.

However, the difference between pirfenidone and placebo for all-cause mortality was not statistically significant after 72 weeks:

- hazard ratio 0.77 when CAPACITY 1 and 2 were pooled, $p=0.315$
- hazard ratio 0.63 when 52-week data from ASCEND and 72-week data from the 2 CAPACITY trials were meta-analysed by the ERG, 95% credible interval 0.38 to 1.07.

The committee heard that the clinical experts could not explain the apparent diminishing effect of pirfenidone on mortality over time in the trials. The committee acknowledged that the hazard ratios suggest a lower risk of death with pirfenidone compared with best supportive care. However, in the analyses with the longest follow-up, the survival benefit of pirfenidone was not statistically significant and so the committee noted that this result could have arisen by chance.

Cost-effectiveness modelling

- 4.9 The committee was aware that the company had presented a different model to that considered in technology appraisal guidance 282. For the present appraisal, the company submitted a partitioned survival model with 3 mutually exclusive health states: progression-free, progressed and dead. The committee heard from the ERG that the company's model was overly simplistic and did not capture the progressive nature of idiopathic

pulmonary fibrosis. The committee noted that the model structure made several clinically implausible assumptions. For example:

- There was no relationship between time on treatment, time to progression (defined as 10% decline in percent predicted FVC, 50 metre decline in 6-minute walking distance, or death) and mortality. The committee agreed that these events were likely to be linked, so it was not appropriate to model them independently.
- Acute exacerbations were 'disconnected' from disease progression and mortality. Clinical experts advised that exacerbations had a substantial impact on quality of life and survival. The committee agreed that the model may have underestimated the impact of exacerbations.

The committee had serious concerns about the company's model and understood that the ERG could address only some of the issues in its exploratory analyses. It would have preferred to see a model that captured the progressive nature of idiopathic fibrosis, and linked clinical outcomes with each other and with time on treatment. The committee concluded that the company's model had serious limitations, some of which could not be resolved by the ERG, and this led to substantial uncertainty about the ICERs.

- 4.10 The committee discussed the company's modelling assumption that the survival benefit of pirfenidone, compared with best supportive care, was constant over a person's lifetime. That is, pirfenidone reduced the risk of death to the same degree early in treatment as after years of treatment. The committee appreciated that the trials were too short to provide evidence to support this assumption. It was also aware that the model was very sensitive to the assumptions around duration of treatment benefit. One clinical expert stated that he expected the treatment benefit of pirfenidone to be constant over a person's lifetime. The committee did not agree that this was plausible, based on advice from the ERG that the clinical trial data showed a reduction in treatment effect over time for

overall survival. It understood that the ERG had modelled an optimistic scenario that used the company's assumption of a constant lifetime benefit, and a pessimistic scenario that stopped the treatment effect after 2 years (approximately at the end of the randomised trial evidence). The committee concluded that the treatment effect of pirfenidone was likely to last somewhere between 2 years and a lifetime.

- 4.11 The committee discussed the estimates of relative clinical effectiveness in the model, noting that the ERG's cost-effectiveness analyses used hazard ratios from an amended network meta-analysis. It understood that the model was sensitive to changing these efficacy inputs. The committee agreed that it preferred to use efficacy estimates from the ERG's network meta-analysis because this included the 72-week follow-up data and used the predictive distribution (see section 4.7). It noted that the ERG's base-case network meta-analysis excluded the SP3 trial, and a scenario including the SP3 data reduced the ICERs for pirfenidone slightly. The committee concluded that its preferred analysis took hazard ratios from the ERG's network meta-analysis including the SP3 trial, for the reasons explained in section 4.7.
- 4.12 The committee discussed the company's choice of parametric curve to estimate survival, which was a key driver of the results. It noted that the company had modelled overall survival using the Weibull distribution, and that the ERG had used the Gompertz distribution. It heard from the ERG that the Weibull curve fitted the observed data well, but that it predicted a lower probability of death for older people than in the general UK population; the ERG did not consider this to be clinically plausible. The ERG considered that the Gompertz distribution also fitted the data well but provided a more clinically plausible long-term extrapolation for overall survival, beyond the observed data. The committee acknowledged the company's different opinion, but agreed that it was more clinically plausible to use the Gompertz distribution to estimate survival.

4.13 The committee was aware that the ERG had made additional changes to the costs and utilities in the company's model, including:

- capping utility estimates at 1.0
- adjusting utility by age
- including costs associated with end of life for all people irrespective of the cause of death
- including dose titration in the first model cycle
- changing the mean dose of nintedanib, based on that seen in the INPULSIS trials of nintedanib
- correcting minor programming errors.

The committee was aware that these changes had a smaller impact on the results than varying the duration of treatment effect, the changes to the network meta-analysis, and the choice of distribution for overall survival. It concluded that these amendments were appropriate.

Cost-effectiveness results

4.14 The committee considered the cost effectiveness of pirfenidone with the new patient access scheme applied. It first considered the population for whom pirfenidone was recommended in NICE [technology appraisal guidance 282](#), that is, people with an FVC between 50% and 80% predicted. The committee was aware that all ICERs presented by the company and the ERG included the reduced discount (higher price) in the company's proposed patient access scheme. It agreed with the assumptions in the ERG's alternative base case (see sections 4.10 to 4.13), except for excluding SP3 data (see section 4.7). Having agreed that the treatment effect of pirfenidone would be longer than 2 years, but would taper off during a person's lifetime, the committee concluded that the most plausible ICERs for pirfenidone in moderate disease lay between the pessimistic and optimistic estimates presented by the ERG in its scenario analysis that included SP3:

- Without a stopping rule for pirfenidone: £36,230–£96,662 per quality-adjusted life year (QALY) gained, compared with best supportive care.
- With a stopping rule for pirfenidone: £25,603–£64,949 per QALY gained, compared with best supportive care.

4.15 The committee agreed that the ICERs without a stopping rule were all substantially above the range that could be considered a cost-effective use of NHS resources, and therefore it could not recommend pirfenidone without a stopping rule. The committee noted that including a stopping rule for pirfenidone substantially reduced the ICERs, that is, improved the cost effectiveness of pirfenidone. However, the committee noted that because the model could not properly account for the stopping rule (see section 4.4), the ICERs presented were underestimates. In addition, it considered that the ICERs were uncertain because of the clinically implausible assumptions in the model, and the structural issues that the ERG could not amend. The committee concluded that, when using the reduced discount (higher price) in the company's proposed access scheme, the most plausible ICER for the moderate subgroup (that is, people with an FVC between 50% and 80% predicted) was above the range that could be considered a cost-effective use of NHS resources.

Expanding the current recommendation to FVC greater than 80%

4.16 The committee discussed whether the effectiveness of pirfenidone varied depending on the severity of disease at the start of treatment. In the original appraisal of pirfenidone, the committee had concluded that pirfenidone was clinically effective for moderate disease. In the current appraisal, the committee decided it had seen no evidence to alter that conclusion. It discussed the results of the company's 2 analyses to compare the effect of pirfenidone on lung function in mild disease with its effect in moderate disease. The committee was aware that the analysis of covariance (ANCOVA) in 2 post-hoc subgroups (people with an FVC above 80% predicted at baseline, and people with an FVC of 80%

predicted or less) suggested that pirfenidone was associated with a statistically significant benefit compared with placebo in both subgroups. However, the committee noted that, in the company's pre-specified analysis across 3 subgroups (percent predicted FVC at baseline more than 80%; between 70% and 80%; and lower than 70%), there was a non-significant tendency for better outcomes in the placebo group than the pirfenidone group among people with a baseline FVC above 80% predicted. The committee was aware of the company's opinion that the analysis with 3 subgroups was not as robust as the ANCOVA method, but the committee agreed that it was not appropriate to disregard a pre-specified analysis. In addition, during the committee meeting, the company could not fully explain the methods of the ANCOVA analysis. The committee understood that the results of the treatment-by-subgroup interaction tests were not significant in either of the subgroup analyses. However, it heard from the ERG that a non-significant interaction test does not conclusively mean that there is no difference in treatment effect between subgroups. The ERG explained that the interaction test may not have been powered to detect a difference between the subgroups. The committee concluded that it did not see robust evidence that pirfenidone is clinically effective in people with mild idiopathic pulmonary fibrosis (that is, an FVC above 80% predicted).

4.17 The committee discussed the ERG's range of cost-effectiveness estimates for people with mild disease (an FVC above 80% predicted), including SP3 data, noting that they were higher than the ICERs for treating moderate disease:

- Without a stopping rule for pirfenidone: £45,921–£170,279 per QALY gained, compared with best supportive care.
- With a stopping rule for pirfenidone: £29,607–£103,893 per QALY gained, compared with best supportive care.

The committee considered that these ICERs were uncertain and were probably underestimated because of the issues discussed in sections 4.15. The committee heard from the ERG that, given that the ICERs were higher in the population with mild disease than in the population with moderate disease (an FVC between 50% and 80% predicted), the ICERs for mild disease would have increased further if the model had included more people with an FVC above 90% predicted (these people were excluded from ASCEND but would be offered treatment in clinical practice). The committee concluded that, when using the reduced discount (higher price) in the company's proposed access scheme, the most plausible ICER for the mild subgroup was above the range that could be considered a cost-effective use of NHS resources.

Committee conclusions

- 4.18 The committee agreed that, based on the evidence submitted, it could not recommend any of the company's proposed changes to NICE's previous guidance on pirfenidone ([technology appraisal guidance 282](#)). The committee did not consider that any significant and substantial health-related benefits had been excluded from the economic model.
- 4.19 The committee was aware that, in NICE's previous guidance, pirfenidone was regarded as cost effective for people with an FVC between 50% and 80% predicted, using the lower price considered in that appraisal. The committee had not seen any evidence that altered that conclusion. Therefore, the committee agreed to uphold the recommendation in the previous technology appraisal guidance using the discount in the original patient access scheme. It concluded that pirfenidone can continue to be recommended as an option for treating idiopathic pulmonary fibrosis only if:
- the person has a FVC between 50% and 80% predicted
 - the company continues to provide pirfenidone with the discount agreed in the patient access scheme for [technology appraisal guidance 282](#)

- pirfenidone is stopped if there is evidence of disease progression (a decline in percent predicted FVC of 10% or more within any 12 month period).

Potential equality issues and the PPRS

4.20 The committee noted the potential equality issue raised by consultees, that restricting treatment based on percent predicted FVC could discriminate against:

- minority ethnic people, particularly people of south Asian family origin
- disabled people who have difficulty standing straight because FVC is expressed as a percentage of the predicted normal value for a person of the same height
- older people because the reference tables are derived from populations under the age of 70 years, whereas the average age of people with idiopathic pulmonary fibrosis is 72 years.

The committee discussed these issues with the clinical experts, noting that:

- The Global Lung Initiative has introduced equations to predict FVC values in minority ethnic groups and, when these equations were used, FVC values for minority ethnic people were comparable to the FVC values of people in clinical trials (most of whom were white). Thus, when using the newer equations, people would not be denied treatment because of their ethnicity.
- For people who cannot stand straight, their armspan (which approximates their height) can be used to calculate percent predicted FVC. Thus, when using this measure people would not be denied treatment because of their disability.
- According to clinical experts, it is difficult to compare the predicted FVC values of older people with the FVC values of people in clinical trials because older people show a wide range of predicted FVC.

The committee recognised the limitations of FVC but understood that, in clinical practice, the wider patient characteristics would be taken into account in interpreting percent predicted FVC. The committee concluded that its recommendations did not discriminate against any groups of people protected by the Equality Act.

4.21 The committee was aware of NICE’s position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014 and, in particular, the PPRS payment mechanism. It accepted the conclusion ‘that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines’. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

Summary of appraisal committee’s key conclusions

TAXXX	Appraisal title: Pirfenidone for treating idiopathic pulmonary fibrosis	Section
Key conclusion		
Pirfenidone continues to be recommended as an option for treating idiopathic pulmonary fibrosis in adults only if: <ul style="list-style-type: none"> • the person has a forced vital capacity (FVC) between 50% and 80% predicted • the company provides pirfenidone with the discount agreed in the patient access scheme for technology appraisal guidance 282 • pirfenidone treatment is stopped if there is evidence of disease progression (a decline in percent predicted FVC of 10% or more 		1.1, 1.2, 1.3, 4.14–4.17

<p>within any 12-month period).</p> <p>The committee discussed the incremental cost-effectiveness ratios (ICERs) for pirfenidone with the reduced discount (higher price) in the company's proposed patient access scheme. For the subgroup with mild disease and the subgroup with moderate disease:</p> <ul style="list-style-type: none"> • It could not recommend pirfenidone without a stopping rule because the ICERs were all substantially above the range that could be considered cost effective. • When considering the ICERs with a stopping rule, it agreed that the ICERs were uncertain and were likely to be higher than the evidence review group's (ERG's) estimates. <p>The committee concluded that, when using the reduced discount, the ICERs for both subgroups were above the range that could be considered cost effective. However, in NICE's previous guidance on pirfenidone, the drug was regarded as cost effective for people with an FVC between 50% and 80% predicted. The committee agreed to uphold the recommendation in the previous guidance.</p>		
Current practice		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>People with an FVC of between 50% and 80% predicted (moderate disease) are offered nintedanib or pirfenidone, and treatment is stopped if FVC deteriorates by 10% or more in a 12-month period (in line with NICE guidance). People with an FVC above 80% predicted (mild disease) are offered best supportive care.</p>	<p>4.5</p>
The technology		

<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The committee did not consider that any significant and substantial health-related benefits had been excluded from the economic model.</p>	<p>4.18</p>
<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>Pirfenidone has a marketing authorisation in the UK for treating mild to moderate idiopathic pulmonary fibrosis in adults.</p>	<p>2.1</p>
<p>Adverse reactions</p>	<p>The very common adverse reactions associated with using pirfenidone are nausea, rash, diarrhoea, fatigue, dyspepsia, anorexia, headache and photosensitivity reaction.</p>	<p>2.2</p>
<p>Evidence for clinical effectiveness</p>		
<p>Availability, nature and quality of evidence</p>	<p>The company's clinical evidence came from 4 randomised double-blind placebo-controlled trials: CAPACITY 1, CAPACITY 2, ASCEND and SP3. The results of SP3 and the CAPACITY trials were considered during the original NICE technology appraisal of pirfenidone. Results from the ASCEND trial were not available then and have prompted this review. The company submitted a network meta-analysis which informed its cost-</p>	<p>4.7</p>

	effectiveness model. The ERG did its own network meta-analysis, which differed from the company's analysis.	
Relevance to general clinical practice in the NHS	ASCEND excluded people with an FVC above 90% predicted. These patients would be considered for treatment in clinical practice (although active treatments are not currently recommended by NICE for these people).	4.17
Uncertainties generated by the evidence	The committee acknowledged that the hazard ratios presented by the company suggest a lower risk of death with pirfenidone compared with best supportive care. However, in the analyses with the longest follow-up, the survival benefit of pirfenidone was not statistically significant and so the committee noted that this result could have arisen by chance.	4.8
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	In the original appraisal of pirfenidone (NICE technology appraisal guidance 282), the committee had concluded that pirfenidone was clinically effective for moderate disease. In the current appraisal, the committee decided it had seen no evidence to alter that conclusion but it did not see robust evidence that pirfenidone is clinically effective in people with mild idiopathic pulmonary fibrosis (that is, an FVC above 80% predicted).	4.16
Estimate of the size of the clinical	The difference between pirfenidone and placebo for all-cause mortality was not	4.16

<p>effectiveness including strength of supporting evidence</p>	<p>statistically significant if the ASCEND or CAPACITY trials were analysed separately.</p> <p>The survival benefit of pirfenidone was statistically significant when combining 52-week all-cause mortality data:</p> <ul style="list-style-type: none"> • hazard ratio 0.49 when CAPACITY 1 and 2 were pooled, p=0.047 • hazard ratio 0.52 when ASCEND and the 2 CAPACITY trials were pooled, p=0.011 • hazard ratio 0.52 when ASCEND, the 2 CAPACITY trials and SP3 were meta-analysed by the company, 95% credible interval 0.30 to 0.89. <p>The difference between pirfenidone and placebo for all-cause mortality was not statistically significant after 72 weeks:</p> <ul style="list-style-type: none"> • hazard ratio 0.77 when CAPACITY 1 and 2 were pooled, p=0.315 • hazard ratio 0.63 when 52-week data from ASCEND and 72-week data from the 2 CAPACITY trials were meta-analysed by the ERG, 95% credible interval 0.38 to 1.07. 	
<p>How has the new clinical evidence that has emerged since the original appraisal (TA282) influenced the current</p>	<p>The changes to NICE’s technology appraisal guidance 282 proposed by the company in light of new clinical data are not recommended, specifically:</p> <ul style="list-style-type: none"> • expanding the population to include people 	<p>1.1, 4.14, 4.17, 4.18</p>

recommendations?	<p>with an FVC above 80% predicted</p> <ul style="list-style-type: none"> • removing the recommendation to stop pirfenidone if the disease progresses • a different patient access scheme for pirfenidone (a higher price). 	
Evidence for cost effectiveness		
Availability and nature of evidence	The company provided a partitioned survival model that comprised 3 mutually exclusive health states: progression-free; progressed; and dead. Overall survival, progression-free survival and time to stopping treatment were modelled independently of each other.	4.9
Uncertainties around and plausibility of assumptions and inputs in the economic model	<p>The company's model was overly simplistic and did not capture the progressive nature of idiopathic pulmonary fibrosis. There were several clinically implausible assumptions in the model:</p> <ul style="list-style-type: none"> • no relationship between overall survival, progression-free survival and time to stopping treatment • constant lifetime survival benefit with pirfenidone, compared with best supportive care. <p>The disconnect between treatment duration and treatment outcomes meant that the model could not fully incorporate treatment stopping rules. The committee concluded that the company's model had serious limitations,</p>	4.4, 4.9

	<p>some of which could not be resolved by the ERG, and this led to substantial uncertainty about the ICERs. Analyses including a stopping rule for pirfenidone underestimated the ICER because of the model structure.</p>	
<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>In the ERG's alternative base case, it adjusted cost and utility estimates, but these changes had a small impact on the cost-effectiveness results.</p> <p>The committee did not consider that any significant and substantial health-related benefits had been excluded from the economic model.</p>	<p>4.13, 4.18</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>Pirfenidone was less cost effective (that is, the ICERs were higher) in the subgroup with mild disease than in the subgroup with moderate disease.</p>	<p>4.17</p>
<p>What are the key drivers of cost effectiveness?</p>	<ul style="list-style-type: none"> • Assumptions about how well pirfenidone works over time (duration of treatment effect). • Whether or not pirfenidone is stopped after 	<p>4.5, 4.10– 4.12</p>

	<p>disease progression (the 'stopping rule').</p> <ul style="list-style-type: none"> • Estimation of treatment effect (using the ERG's amended network meta-analysis instead of the company's). • The method for extrapolating overall survival beyond the observed data. 	
<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The committee agreed with the assumptions in the ERG's alternative base case, except for excluding SP3 data. Having agreed that the treatment effect of pirfenidone would be longer than 2 years, but would taper off during a person's lifetime, the committee concluded that the most plausible ICERs for pirfenidone lay between the pessimistic and optimistic estimates presented by the ERG in its scenario analysis that included SP3. All ICERs included the reduced discount (higher price) in the company's proposed patient access scheme.</p> <p>The ICERs for people with an FVC between 50% and 80% predicted (moderate disease) were:</p> <ul style="list-style-type: none"> • Without a stopping rule for pirfenidone: £36,230–£96,662 per quality adjusted life year (QALY) gained, compared with best supportive care. • With a stopping rule for pirfenidone: £25,603–£64,949 per QALY gained, compared with best supportive care. <p>The ICERs for people with an FVC above</p>	<p>4.10– 4.15, 4.17</p>

	<p>80% predicted were higher than the ICERs for treating moderate disease:</p> <ul style="list-style-type: none"> • Without a stopping rule for pirfenidone: £45,921–£170,279 per QALY gained, compared with best supportive care. • With a stopping rule for pirfenidone: £29,607–£103,893 per QALY gained, compared with best supportive care. <p>The committee agreed that the ICERs were uncertain and were likely to be higher than the ERG’s estimates.</p>	
How has the new cost-effectiveness evidence that has emerged since the original appraisal (TA282) influenced the current recommendations?	<p>When using the reduced discount (higher price) in the company’s proposed patient access scheme, the ICERs were above the range that could be considered cost effective. However, in NICE’s previous guidance on pirfenidone (technology appraisal guidance 282), the drug was regarded as cost effective for people with an FVC between 50% and 80% predicted. The committee agreed to uphold the recommendations in the previous technology appraisal guidance using the discount in the original patient access scheme.</p>	4.14, 4.15, 4.17, 4.19
Additional factors taken into account		
Patient access schemes (PPRS)	<p>During the original NICE appraisal of pirfenidone (technology appraisal guidance 282), the company agreed a patient</p>	2.3

	<p>access scheme with the Department of Health. This scheme provides a simple discount to the list price of pirfenidone, with the discount applied at the point of purchase or invoice. The company subsequently proposed that the patient access discount for pirfenidone would be reduced (that is, the price would be higher). The Department of Health agreed that the reduced discount could be taken into account in the present appraisal. The level of both discounts is commercial in confidence.</p>	
End-of-life considerations	Not applicable.	-
Equalities considerations and social value judgements	<p>The committee noted the potential equality issue raised by consultees, that restricting treatment based on percent predicted FVC could discriminate against minority ethnic people, older people and disabled people. The committee discussed these issues with the clinical experts and concluded that its recommendations did not discriminate against any groups of people protected by the Equality Act.</p>	4.20

5 Implementation

- 5.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning

groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has idiopathic pulmonary fibrosis and the doctor responsible for their care thinks that pirfenidone is the right treatment, it should be available for use, in line with NICE's recommendations.

5.4 The Department of Health and Roche Products have agreed that pirfenidone will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to **[NICE to add details at time of publication]**

6 Proposed date for review of guidance

6.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, appraisal committee
May 2016

7 Appraisal committee members, guideline representatives and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee B](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes](#) of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Sophie Laurenson

Technical Lead

Rosie Lovett

Technical Adviser

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ISBN: **[to be added at publication]**