Pirfenidone for treating idiopathic pulmonary fibrosis

This premeeting briefing is a summary of:
- the evidence and views submitted by the manufacturer, which comprises an evidence submission in December 2011 plus an addendum in August 2012 (note that this document describes the content of the original submission except where explicitly stated otherwise)
- the evidence and views submitted by the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report (including an addendum that critiques the additional evidence submitted by the manufacturer in August 2012).

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal. Please note that this document is a summary of the information available before the manufacturer has checked the ERG report’s addendum for factual inaccuracies.

Key issues for consideration

Clinical effectiveness
- Pirfenidone’s UK marketing authorisation is for the treatment of mild to moderate idiopathic pulmonary fibrosis but these levels of disease severity are not defined. The manufacturer’s clinical trials enrolled patients who had a percent predicted forced vital capacity (FVC) of at least 50% at baseline. The manufacturer’s submission cites a study suggesting that threshold FVCs for mild and moderate disease would be defined by a percent predicted FVC of at least 70% and 50% respectively, but the manufacturer presented results for a subgroup of patients with baseline FVC of 80% predicted or less. What is the Committee’s view on the definition of mild to moderate disease?
- The ERG noted that the severity of idiopathic pulmonary fibrosis may be milder in the clinical trials than in UK clinical practice because the mean
baseline FVC values were 73–81% across the 4 randomised controlled trials. Does the Committee consider that the clinical trial results can be applied to the UK population?

- The patient population in the manufacturer’s clinical trials had relatively few comorbidities. Clinical advice to the ERG suggested that people with idiopathic pulmonary fibrosis are likely to have significant comorbidities that would contribute to mortality. Does the Committee consider that the patient population in the clinical trials is generalisable to routine clinical practice in the UK despite the lack of comorbidities?

- No guidance on continuation of therapy is provided in the UK marketing authorisation. The manufacturer’s submission does not describe when it would be appropriate to stop treatment and the ERG noted that treatment discontinuation owing to lack of efficacy was not specified. What is the Committee’s view on treatment discontinuation?

- The manufacturer’s pooled analysis showed an absolute difference of 2.5% in percent predicted FVC at 72 weeks between the pirfenidone and placebo groups. The ERG reported that a decline in FVC of at least 10% in an individual was considered to be an accepted threshold for a clinically significant change, but that a clinically significant effect in a cohort is likely to be lower. Does the Committee consider the difference in per cent predicted FVC at 72 weeks with pirfenidone to be clinically meaningful?

- The manufacturer’s submission shows statistical differences that favour pirfenidone for several outcomes (including the primary outcome) in the PIPF-004 study but not the near-identical PIPF-006 study. Neither the manufacturer nor the ERG was able to find a clear reason for the discrepancy in results between the trials. Is the Committee satisfied that the manufacturer’s pooled analysis provides an acceptable estimate of pirfenidone’s treatment effect?

- The manufacturer presented a subgroup analysis of patients with baseline FVC of 80% predicted or less. The ERG noted uncertainty in interpreting
the results of this subgroup. Does the Committee find this subgroup to be plausible?

- The manufacturer presented a subgroup analysis of patients with baseline FVC of 80% predicted or less excluding patients with borderline obstructive disease, which was defined as an FEV₁/FVC ratio of less than 0.8 (where FEV₁ is forced expired volume in 1 second). ‘Chronic obstructive pulmonary disease’ (NICE clinical guideline 101) defines airflow obstruction as FEV₁/FVC less than 0.7. Does the Committee find this subgroup to be plausible?

Cost effectiveness

- The manufacturer has assumed in its economic model that best supportive care is equivalent to placebo. Does the Committee consider this assumption acceptable?

- The UK marketing authorisation is for the treatment of mild to moderate idiopathic pulmonary fibrosis; however, in the manufacturer’s economic model, treatment is continued until death. Does the Committee consider this to be an acceptable approach?

- The manufacturer’s economic model assumes that pirfenidone’s treatment effect persists over a lifetime horizon. Does Committee find this assumption acceptable?

- The manufacturer’s economic model assumes that the risk of death unrelated to idiopathic pulmonary fibrosis is the same as the general population, which the ERG found acceptable. However, the ERG noted that the manufacturer’s submission does not define which causes of death would be considered related to idiopathic pulmonary fibrosis. Does the Committee find this approach acceptable?

- The manufacturer has calculated the cost effectiveness of pirfenidone compared with triple therapy. The ERG has noted concerns about the validity of the clinical data from the PANTHER study and how these have been incorporated into the manufacturer’s updated model. Does the
Committee consider the cost-effectiveness estimates for the comparison of pirfenidone and triple therapy to be reliable?

- The manufacturer has evaluated the cost effectiveness of pirfenidone compared with a pooled comparator that combines the predicted relative use of best supportive care and triple therapy. The ERG noted that a pooled comparator was not included in the decision problem and that a fully incremental analysis of best supportive care and triple therapy (both specified in the decision problem) provided information that was more valuable for health technology assessment. What is the Committee’s opinion of the pooled comparator?

1 **Background: Clinical need and practice**

1.1 Idiopathic pulmonary fibrosis is a progressive and fatal disease characterised by scarring (or fibrosis) of lung tissue. The cause of idiopathic pulmonary fibrosis is unknown, although its development is associated with a number of factors including cigarette smoking and family history.

1.2 The incidence of idiopathic pulmonary fibrosis is around 8–9 per 100,000 person years, with more than 4000 people diagnosed in the UK each year. An average hospital with a catchment of 500,000 will have 35 new cases a year and an average GP surgery with 10,000 patients will have 2 new cases every 3 years. The median age of presentation is 70 years and the condition is rare in people younger than 45 years.

1.3 The main symptom is breathlessness but a persistent cough, fatigue and weight loss are also common. Symptoms become progressively worse as lung function declines. The natural history of idiopathic pulmonary fibrosis is characterised by periods of relative stability, which may be interspersed with episodes of stepwise deterioration in symptoms. Disease progression is
1.4 The aim of treatment is to manage symptoms and slow progression, with treatment options dependent on the stage and severity of the disease. There are few effective treatments for the symptoms of idiopathic pulmonary fibrosis, and presently only pirfenidone has a UK marketing authorisation for this condition. Triple therapy with prednisolone, azathioprine and N-acetylcysteine may be offered to some people. Best supportive care may involve smoking cessation, oxygen therapy, pulmonary rehabilitation, opiates, antireflux therapy, corticosteroids and other immunosuppressants, and palliative care. Some people do not receive treatment at all and a minority may be eligible for a lung transplant. A NICE clinical guideline on idiopathic pulmonary fibrosis is in development, with publication expected in June 2013.

2 The technology

2.1 Pirfenidone (Esbriet, InterMune) is an immunosuppressant that is thought to have anti-inflammatory and antifibrotic effects. Its mechanism of action is not fully understood but it is likely that pirfenidone exerts its effects by suppressing fibroblast proliferation, reducing the production of fibrosis-associated proteins and cytokines and reducing the response to growth factors such as transforming growth factor-beta (TGF-β) and platelet-derived growth factor (PDGF). Pirfenidone has a UK marketing authorisation for the treatment of mild to moderate idiopathic pulmonary fibrosis in adults. The recommended dosage of pirfenidone is 3×267 mg capsules 3 times a day (2403 mg/day).

2.2 The summary of product characteristics lists the following adverse reactions for pirfenidone as the most commonly reported (10% or
higher): nausea, rash, fatigue, diarrhoea, dyspepsia and photosensitivity reaction. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Pirfenidone is priced at £501.92 for a 14-day, 63-capsule starter pack, £2007.70 for a 28-day, 252-capsule blister pack and £2151.10 for a 30-day, 270-capsule bottle (all excluding VAT). The annual cost of ongoing treatment is £26,171.72, assuming no wastage. Costs may vary in different settings because of negotiated procurement discounts.

3 Remit and decision problem

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of pirfenidone within its licensed indication for the treatment of idiopathic pulmonary fibrosis.
### Decision problem addressed in the manufacturer’s submission

<table>
<thead>
<tr>
<th><strong>Population</strong></th>
<th>People with mild to moderate idiopathic pulmonary fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td>Pirfenidone</td>
</tr>
<tr>
<td><strong>Comparators</strong></td>
<td>• Best supportive care</td>
</tr>
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<td></td>
<td>• Triple therapy with prednisolone, azathioprine and N-acetylcysteine</td>
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<tr>
<td><strong>Outcomes</strong></td>
<td>• Pulmonary function parameters</td>
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<tr>
<td></td>
<td>- Forced vital capacity (FVC) or vital capacity (VC)</td>
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<td></td>
<td>- Diffusing capacity of the lung for carbon monoxide (DL\textsubscript{CO})</td>
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<td>- Worst peripheral oxygen saturation (SpO\textsubscript{2}) during the 6-minute walk test</td>
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<td>• Physical function</td>
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<td>• Progression-free survival</td>
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<td>• Exacerbation rate</td>
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<td>• Adverse effects of treatment</td>
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<td>• Mortality</td>
</tr>
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<td>• Health-related quality of life</td>
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<tr>
<td><strong>Economic evaluation</strong></td>
<td>Incremental cost per quality-adjusted life year.</td>
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<tr>
<td></td>
<td>The time horizon considered is lifetime. Costs will be considered from an NHS and personal social services perspective.</td>
</tr>
</tbody>
</table>

3.2 The decision problem in the manufacturer’s original submission (December 2011) was in line with the final scope issued by NICE, except that triple therapy with prednisolone, azathioprine and N-acetylcysteine had been excluded. The manufacturer stated that it did not include triple therapy because the US National Institutes for Health recently announced that the triple-therapy arm of the PANTHER study (triple therapy compared with N-acetylcysteine alone compared with placebo) had been terminated after excess mortality. In an addendum submitted in August 2012, the manufacturer acknowledged the uncertainty around the continuing use of triple therapy in the NHS and included triple therapy as a comparator, making the decision problem identical to that in the final scope. The ERG noted in its original report that it had received clinical advice that triple therapy is unlikely to be a main comparator because of the reason originally given by the manufacturer, plus
previous consensus in the clinical community that it had limited use.

3.3 The manufacturer noted that although the decision problem specified best supportive care as a comparator, all relevant randomised controlled trials compared pirfenidone with placebo. The manufacturer advised that many elements of best supportive care were available to patients in both the pirfenidone and placebo arms of the randomised controlled trials. It noted, however, that use of corticosteroids and immunosuppressants were exclusion criteria for the trials.

3.4 The manufacturer advised that it anticipates pirfenidone will be used directly after diagnosis of idiopathic pulmonary fibrosis.

4 Clinical-effectiveness evidence

4.1 The manufacturer presented 4 randomised studies in its submission, comprising 3 phase III studies (PIPF-004, PIPF-006 and SP3) and a phase II study (SP2). Two randomised phase II studies were excluded because the manufacturer noted

Of the 4 non-randomised clinical trials identified, 2 were excluded by the manufacturer because they were not relevant to the decision problem. Interim data were included from an open-label extension study (PIPF-012, which is an extension of PIPF-004 and PIPF-006 and is expected to complete in 2015) and a safety study (PIPF-002).

4.2 PIPF-004 and PIPF-006 (also known as CAPACITY-2 and CAPACITY-1) had near-identical methodology and investigated the effect of treatment with pirfenidone for 72 weeks in adults aged 40–80 years with mild to moderate idiopathic pulmonary fibrosis (FVC
at least 50% predicted and DL_{CO} at least 35% predicted at screening). In PIPF-004, patients received pirfenidone 1197 mg/day (n=87), pirfenidone 2403 mg/day (n=174) or placebo (n=174). In PIPF-006, patients received pirfenidone 2403 mg/day (n=171), or placebo (n=173). The manufacturer explained that the dosage of 2403 mg/day was chosen to provide a similar dose per kg body weight in a North American and European patient population as the lower dose used in the phase II SP2 study in a Japanese population. Both trials were conducted in Australia, Europe and North America and were regarded as pivotal by the Committee for Medicinal Products for Human Use. The manufacturer indicated that baseline characteristics were generally similar in the different arms of the studies, although some differences were noted between patients from the USA and patients from the rest of the world (see page 65 of the manufacturer’s submission for details).

4.3 In SP3, which was conducted in Japan, adults aged 20–75 years with idiopathic pulmonary fibrosis received pirfenidone 1200 mg/day (n=55), pirfenidone 1800 mg/day (n=108) or placebo (n=104) for 52 weeks. In SP2, which was also conducted in Japan, adults aged 20–75 years with idiopathic pulmonary fibrosis received pirfenidone 1800 mg/day (n=72) or placebo (n=35) for 36 weeks (out of a planned 48 weeks). In an ongoing open-label extension study (PIPF-012), a total of 603 patients who had completed either PIPF-004 or PIPF-006 received pirfenidone 2403 mg/day. These patients had been previously treated with pirfenidone 2403 mg/day (n=261), pirfenidone 1197 mg/day (n=68) or placebo (n=274). In an ongoing non-controlled long-term study (PIPF-002), patients (n=83) received pirfenidone at a dosage of up to 3600 mg/day.
The primary outcomes of the studies were baseline-to-end point change in per cent predicted FVC (PIPF-004 and PIPF-006) or VC (SP3 study), change in SpO\textsubscript{2} during the 6-minute walk test (SP2 study), and safety (PIPF-012 and co-primary end point in PIPF-002). Secondary outcomes included progression-free survival, categorical FVC, worsening of disease (time to acute exacerbation, death, lung transplantation, or respiratory-related hospitalisation), per cent predicted DL\textsubscript{CO}, 6-minute walk test, worst SpO\textsubscript{2} during the 6-minute walk test and dyspnoea. Quality of life was assessed in PIPF-004, PIPF-006 and SP2. Overall survival was an exploratory end point in PIPF-004 and PIPF-006. The analysis of each study was based on the intention-to-treat populations, whereas the pooled analysis used the intention-to-treat pooled population of PIPF-004 and PIPF-006. Results from PIPF-004 using the unlicensed dosage of pirfenidone (1197 mg/day), have not been included in this document.

**Efficacy results from the pivotal studies**

*Intention-to-treat analyses*

4.5 The manufacturer’s results for change in per cent predicted FVC from PIPF-004, PIPF-006 and a pooled analysis of the 2 studies are shown in table 1. There was a statistically significant difference in the decline in per cent predicted FVC between pirfenidone 2403 mg/day and placebo groups in PIPF-004 and in the pooled analysis, but not in PIPF-006. Analysis of change in per cent predicted FVC at 12-week intervals from baseline to end point showed a significant reduction in the decline in per cent predicted FVC with pirfenidone 2403 mg/day compared with placebo at every time point from week 12 onwards in the pooled analysis and from week 24 onwards in PIPF-004. In PIPF-006, there was a significant difference in favour of pirfenidone 2403 mg/day from week 24 to
week 48 but not at the later time points. At week 12 in PIPF-006, the analysis favoured placebo.

Table 1 Primary end point results from PIPF-004, PIPF-006 and a pooled analysis of the 2 studies: baseline to end point mean change in per cent predicted FVC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Pirfenidone 2403 mg/day</th>
<th>Placebo</th>
<th>Absolute difference</th>
<th>Relative difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIPF-004</td>
<td>-8.0% (n=174)</td>
<td>-12.4% (n=174)</td>
<td>4.4%</td>
<td>35.3%</td>
<td>p=0.001</td>
</tr>
<tr>
<td>PIPF-006</td>
<td>-9.0% (n=171)</td>
<td>-9.6% (n=173)</td>
<td>0.6%</td>
<td>6.5%</td>
<td>p=0.501</td>
</tr>
<tr>
<td>Pooled analysis</td>
<td>-8.5% (n=345)</td>
<td>-11.0% (n=347)</td>
<td>2.5%</td>
<td>22.8%</td>
<td>p=0.005</td>
</tr>
</tbody>
</table>

Key: FVC, forced vital capacity
Source: Manufacturer’s original submission, page 94

4.6 The manufacturer presented results for a categorical assessment of absolute change in per cent predicted FVC in a pooled analysis of PIPF-004 and PIPF-006. It noted that fewer patients who received pirfenidone 2403 mg/day experienced a decline in per cent predicted FVC of 10% or greater compared with those receiving placebo (21.5% and 30.5% of patients).

4.7 The manufacturer reported that there was no consistent treatment effect for several secondary efficacy variables that measured baseline to end point changes in PIPF-004 and PIPF-006, including worst SpO$_2$ in the 6-minute walk test, per cent predicted DL$_{CO}$, dyspnoea and time to worsening of idiopathic pulmonary fibrosis. The manufacturer’s original submission stated that there was no significant difference in mean change in 6-minute walk test distance at 72 weeks between the pirfenidone 2403 mg/day and placebo groups in PIPF-004 (absolute difference of 16.4 metres); however, there was a significant difference between the groups in PIPF-006 (absolute difference of 31.8 metres) and in the pooled analysis (absolute difference of 24.0 metres). The manufacturer noted that
the minimal clinically important difference has been estimated at 24–45 and 28 metres in 2 recent studies.

4.8 The manufacturer found that there was no significant difference in time to worsening of idiopathic pulmonary fibrosis between the pirfenidone 2403 mg/day and placebo groups in PIPF-004 (hazard ratio 0.84, 95% confidence interval [CI] 0.50 to 1.42, p=0.515) or PIPF-006 (hazard ratio 0.73, 95% CI 0.43 to 1.24, p=0.248).

Worsening was defined as the first occurrence of acute exacerbation, respiratory-related hospitalisation, lung transplantation or death related to idiopathic pulmonary fibrosis.

4.9 The manufacturer presented results for progression-free survival, which was defined as time to confirmed decline of at least 10% in per cent predicted FVC (which it advised was a threshold widely accepted as clinically meaningful and prognostic of death), a decline of at least 15% in per cent predicted DLCO, or death (table 2). In PIPF-004 and in the pooled analysis, but not PIPF-006, there was a significant reduction in the risk of death or disease progression with pirfenidone 2403 mg/day compared with placebo.
Table 2 Progression-free survival in PIPF-004, PIPF-006 and a pooled analysis of the 2 studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Death or disease progression</th>
<th>Disease progression with decline in FVC</th>
<th>Disease progression with decline in DL(_{CO})</th>
<th>Death before disease progression</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIPF-004</td>
<td></td>
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<tr>
<td>Pirfenidone</td>
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<tr>
<td>2403 mg/day</td>
<td>45/172 (26.2%)</td>
<td>28 (16.3%)</td>
<td>9 (5.2%)</td>
<td>8 (4.7%)</td>
<td>0.64</td>
<td>(0.44 to 0.95)</td>
</tr>
<tr>
<td>Placebo</td>
<td>62/173 (35.8%)</td>
<td>39 (22.5%)</td>
<td>9 (5.2%)</td>
<td>14 (8.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIPF-006</td>
<td></td>
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<tr>
<td>Pirfenidone</td>
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<tr>
<td>2403 mg/day</td>
<td>54/170 (31.8%)</td>
<td>31 (18.2%)</td>
<td>10 (5.9%)</td>
<td>13 (7.6%)</td>
<td>0.84</td>
<td>(0.58 to 1.22)</td>
</tr>
<tr>
<td>Placebo</td>
<td>60/172 (34.9%)</td>
<td>41 (23.8%)</td>
<td>9 (5.2%)</td>
<td>10 (5.8%)</td>
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<td></td>
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<tr>
<td>Pooled analysis</td>
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<tr>
<td>Pirfenidone</td>
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<tr>
<td>2403 mg/day</td>
<td>99/342 (28.9%)</td>
<td>59 (17.3%)</td>
<td>19 (5.6%)</td>
<td>21 (6.1%)</td>
<td>0.74</td>
<td>(0.57 to 0.96)</td>
</tr>
<tr>
<td>Placebo</td>
<td>122/345 (35.4%)</td>
<td>80 (23.2%)</td>
<td>18 (5.2%)</td>
<td>24 (7.0%)</td>
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</tbody>
</table>

Key: CI, confidence interval; DL\(_{CO}\), diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; HR, hazard ratio
Source: Manufacturer’s original submission, page 103

4.10 The manufacturer presented an exploratory analysis of overall survival for all patients, which showed that less than 10% of patients died in PIPF-004 and PIPF-006. Furthermore, there was no statistically significant difference in the risk of death between the pirfenidone 2403 mg/day and placebo groups in PIPF-004 (hazard ratio 0.61 [95% CI 0.28 to 1.29], p=0.191), PIPF-006 (hazard ratio 0.95 [95% CI 0.48 to 1.87], p=0.872) and the pooled analysis (hazard ratio 0.77 [95% CI 0.47 to 1.28], p=0.315). The manufacturer calculated that the hazard ratio for mortality related to idiopathic pulmonary fibrosis up to 72 weeks (time point for the primary outcome) was 0.53 (95% CI 0.288 to 1.028, p=0.0606). Because of low patient numbers for follow-up beyond this time, the manufacturer considered this value to be the most robust in calculating pirfenidone’s overall treatment effect and implemented it in its economic model.
4.11 The manufacturer described a further (ad hoc) analysis of overall survival in relation to the treatment-emergent deaths in PIPF-004, PIPF-006 and the pooled analysis. The time period of this analysis is not clear. Treatment-emergent deaths were defined as deaths that occurred after the first dose and within 28 days of the last dose of study treatment. The manufacturer reported that there was no difference in all treatment-emergent deaths between the pirfenidone 2403 mg/day and placebo groups in PIPF-004, PIPF-006 and the pooled analysis. A statistically significant reduction in the risk of treatment-emergent deaths related to idiopathic pulmonary fibrosis was noted in the manufacturer’s pooled analysis but not in the individual PIPF-004 and PIPF-006 studies (table 3).

Table 3 Overall survival: treatment-emergent deaths in PIPF-004, PIPF-006 and a pooled analysis of the 2 studies

<table>
<thead>
<tr>
<th>Study</th>
<th>All treatment-emergent deaths</th>
<th>Treatment-emergent deaths related to idiopathic pulmonary fibrosis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Patient death n (%)</td>
<td>Patients censored n (%)</td>
</tr>
<tr>
<td>PIPF-004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pirfenidone (n=174)</td>
<td>10 (5.7%)</td>
<td>164 (94.3%)</td>
</tr>
<tr>
<td>Placebo, (n=174)</td>
<td>14 (8.0%)</td>
<td>160 (92%)</td>
</tr>
<tr>
<td>PIPF-006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pirfenidone (n=171)</td>
<td>9 (5.3%)</td>
<td>162 (94.7%)</td>
</tr>
<tr>
<td>Placebo (n=173)</td>
<td>15 (8.7%)</td>
<td>158 (91.3%)</td>
</tr>
<tr>
<td>Pool analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pirfenidone (n=345)</td>
<td>19 (5.5%)</td>
<td>326 (94.5%)</td>
</tr>
<tr>
<td>Placebo (n=347)</td>
<td>29 (8.4%)</td>
<td>318 (91.6%)</td>
</tr>
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</table>

Key: CI, confidence interval; HR, hazard ratio
Source: Manufacturer's original submission, page 107

4.12 Data presented by the manufacturer showed that there was no difference in change in dyspnoea (measured using the University of California at San Diego Shortness-of-Breath Questionnaire) between the pirfenidone 2403 mg/day and placebo groups in
PIPF-004, PIPF-006 and the pooled analysis. The manufacturer also presented exploratory analyses of quality of life in PIPF-004 and PIPF-006.

4.13 The manufacturer stated that no instrument specific to idiopathic pulmonary fibrosis was available when the study started, so respiratory status was measured using the St George’s Respiratory Questionnaire that was designed and validated for patients with chronic obstructive pulmonary disease. However, after recent validation and publication of a version of the questionnaire for idiopathic pulmonary fibrosis, the manufacturer conducted a post-hoc analysis of the intention-to-treat population of PIPF-004 and PIPF-006.

The manufacturer noted that the most recent estimates of a minimum clinically meaningful change in St George’s Respiratory Questionnaire score are 5–8 points, whereas this was previously defined as 4 points.

4.14 The manufacturer provided a post-hoc analysis of hospitalisations in PIPF-004 and PIPF-006, which demonstrated that the number of hospitalisations for respiratory and non-respiratory reasons for patients receiving pirfenidone 2403 mg/day (51 out of 345 patients had at least 1 hospitalisation) and those receiving placebo (52 out of 347 patients had at least 1 hospitalisation) were similar. However, it reported that the mean duration of stay in hospital for
was lower for the pirfenidone group than for the placebo group for respiratory-related reasons (8.0 days compared with 14.6 days) and for non-respiratory reasons (8.8 days and 18.0 days).

Subgroup analyses

4.15 The manufacturer analysed the primary outcome results for per cent predicted FVC according to subgroups defined by baseline patient characteristics (for the forest plots, see the manufacturer’s original submission, pages 96–98). The manufacturer reported that the subgroup analyses favoured pirfenidone 2403 mg/day in most subgroups in PIPF-004 and PIPF-006, but noted that the confidence intervals crossed the line of no effect for all subgroups in PIPF-006, indicating no treatment effect. In the pooled analysis, the manufacturer noted that was no evidence of interaction between treatment and gender, age, race, geographic region and baseline severity of disease. However, it concluded there was evidence of an effect favouring pirfenidone in patients with a baseline FVC of less than 80% predicted (no numerical data or statistical analyses were provided in the original submission to support this statement; see section 4.39 for ERG’s comment).

4.16 Using the pooled data, the manufacturer also performed analyses of the absolute differences in the change in per cent predicted FVC between pirfenidone 2403 mg/day and placebo for these subgroups (see page 99 of the manufacturer’s original submission). The manufacturer’s submission did not provide an interpretation of the graph. However, the Food and Drug Administration (FDA) briefing for the Pulmonary Advisory Committee, which was the supporting reference provided by the manufacturer, describes how these analyses showed variation in the size of the treatment effect in these subgroups but all favoured the pirfenidone group, except for patients with a baseline FVC of 80% predicted or higher.
Statistically significant interactions were observed between treatment and the time from diagnosis to randomisation, and between treatment and baseline supplemental oxygen use during the 6-minute walk test.

4.17 In its addendum, the manufacturer provided further details of the analysis of the primary outcome results for per cent predicted FVC in the subgroup of patients in PIPF-004 and PIPF-006 who had a baseline FVC of 80% predicted or less. This subgroup was considered by the manufacturer because decreased lung function is associated with increased risk of death and it wished to understand whether patients with a lower per cent predicted FVC would gain greater benefit from pirfenidone treatment. The manufacturer reported that, in patients with baseline FVC of 80% predicted or less, the decrease observed in per cent predicted FVC was statistically significantly lower at all time points up to 72 weeks with pirfenidone compared with placebo, and this was clinically significant. However, the manufacturer noted that statistically significant differences between the pirfenidone and placebo groups were not observed at all time points in patients with baseline per cent predicted FVC greater than 80% (see table 4 and page 8 of the manufacturer’s addendum).

Table 4 Baseline to 72-week end point mean change in per cent predicted FVC (pooled analysis of PIPF-004 and PIPF-006): subanalysis by baseline per cent predicted FVC

<table>
<thead>
<tr>
<th></th>
<th>Pirfenidone 2403 mg/day (n=244)</th>
<th>Placebo (n=233)</th>
<th>Absolute difference</th>
<th>Relative difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline FVC ≤80% predicted</td>
<td>−8.4%</td>
<td>−12.7%</td>
<td>4.3%</td>
<td>33.7%</td>
<td>p=0.0052</td>
</tr>
<tr>
<td>Baseline FVC &gt;80% predicted</td>
<td>−8.6%</td>
<td>−7.4%</td>
<td>−1.1%</td>
<td>−15.4%</td>
<td>p=0.2979</td>
</tr>
</tbody>
</table>

Key: FVC, forced vital capacity
Source: Manufacturer’s addendum, page 8
4.18 In its addendum, the manufacturer provided an analysis of other outcome results in the subgroup of patients in PIPF-004 and PIPF-006 who had a baseline FVC of 80% predicted or less. The manufacturer indicated that there was a statistically significant reduction in the risk of disease progression or death, all-cause mortality and mortality related to idiopathic pulmonary fibrosis for patients receiving pirfenidone compared with placebo in this subgroup (table 5).

Table 5 Progression-free survival and mortality (pooled analysis of PIPF-004 and PIPF-006): subanalysis by baseline FVC

<table>
<thead>
<tr>
<th></th>
<th>Pirfenidone 2403 mg/day (n=244)</th>
<th>Placebo (n=233)</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression-free survival</td>
<td>68 (28.2%)</td>
<td>83 (35.8%)</td>
<td>0.68 (0.49 to 0.94)</td>
<td>p=0.0196</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>19 (7.8%)</td>
<td>31 (13.3%)</td>
<td>0.56 (0.31 to 0.99)</td>
<td>p=0.0424</td>
</tr>
<tr>
<td>Mortality related to idiopathic pulmonary fibrosis</td>
<td>12 (4.9%)</td>
<td>28 (12.0%)</td>
<td>0.39 (0.20 to 0.77)</td>
<td>p=0.0048</td>
</tr>
</tbody>
</table>

Key: CI, confidence interval; FVC, forced vital capacity
Source: Manufacturer’s addendum page 9

**Efficacy results from other randomised studies**

4.19 In the SP3 study, the manufacturer’s submission states that treatment with pirfenidone 1800 mg/day was associated with a reduced decline in VC at 52 weeks compared with placebo (−0.09 litres compared with −0.16 litres, p=0.042). Similar results were observed with pirfenidone 1200 mg (−0.08 litres compared with −0.16 litres, p=0.0394). The manufacturer reported that there was no difference between the 2 pirfenidone groups. The manufacturer’s analysis of progression-free survival showed that pirfenidone 1800 mg/day significantly reduced the risk of death or disease progression, which was defined as a decline in VC of at least 10% (hazard ratio 0.45, 95% CI 0.11 to 0.79, p=0.028). The
manufacturer indicated that results for the pirfenidone 1200 mg/day group were similar to those with the higher dosage.

4.20 For the SP2 study, the manufacturer’s submission describes how the primary end point at 48 weeks was not reached in the full analysis set (n=107) because the study was abandoned after an interim analysis that showed a high rate of acute exacerbations in the placebo group. Mean change in worst SpO₂ during the 6-minute walk test was similar in the pirfenidone and placebo groups at 6 months (+0.64% compared with −0.55%, p=0.1489) and at 9 months (+0.47% compared with −0.94%, p=0.0722). However, the manufacturer reported a significant difference between groups in patients (n=80) who had completed the 6-minute walk test at baseline (p=0.0069 at 6 months and p=0.0305 at 9 months). Secondary outcomes generally favoured pirfenidone, but the manufacturer indicated that quality of life and dyspnoea were not affected by the study medication.

**Indirect comparison**

4.21 In its addendum, the manufacturer performed an indirect comparison of pirfenidone with triple therapy using the interim results for the placebo and triple-therapy arms of the PANTHER study, which had been published since the original submission. The manufacturer calculated indirect hazard ratios for pirfenidone compared with triple therapy by multiplying the all-cause mortality hazard ratio from the PANTHER study at 60 weeks by the hazard ratio for the mortality related to idiopathic pulmonary fibrosis in PIPF-004 and PIPF-006. The manufacturer reported that this gave a hazard ratio of 0.06 for the total pooled patient population for PIPF-004 and PIPF-006, and a hazard ratio of 0.04 for the subgroup of patients with baseline FVC of 80% predicted or less.
Meta-analyses

4.22 The manufacturer stated in its original submission that it could not carry out a network meta-analysis of pirfenidone compared with triple therapy with prednisolone, azathioprine and N-acetylcysteine because of limitations in the data from randomised controlled trials. The reasons provided included the lack of a placebo arm in the IFEGNIA study (which evaluated triple therapy compared with corticosteroids and azathioprine alone) and the early termination of the triple-therapy arm in the ongoing PANTHER study (comparing triple therapy with N-acetylcysteine alone and with placebo).

4.23 The manufacturer provided several meta-analyses from a total of 997 patients. The analyses generally combined outcomes from PIPF-004, PIPF-006 and SP3, or from PIPF-004 and PIPF-006. The meta-analyses combined data from PIPF-004 and PIPF-006 using the dosage of pirfenidone that is licensed in the UK (2403 mg/day) and from SP2 and SP3 at the dosage of pirfenidone that is licensed in Japan (1800 mg/day). The manufacturer considered this to be appropriate because the dose by weight would be similar for all studies. Furthermore, the manufacturer indicated that FVC (the primary outcome for PIPF-004 and PIPF-006) and VC (the primary outcome for SP3) were similar and could be combined.

4.24 In a meta-analysis of FVC and VC, the manufacturer reported a

using a random-effects model for the 3 pooled phase III trials. A treatment effect of 0.20 (95% CI 0.05 to 0.35, p=0.01) was observed using a fixed-effects model for PIPF-004 and PIPF-006 alone. The manufacturer identified

substantial heterogeneity when PIPF-004 and PIPF-006 were
combined ($I^2=71\%$). The manufacturer was unable to determine the reason for the heterogeneity between the 2 near-identical trials for FVC and VC (discussed on pages 127–128 of the manufacturer’s original submission). Meta-analyses for several other outcomes are presented on pages 132–138 of the manufacturer’s original submission.

4.25 In its addendum, the manufacturer presented meta-analyses for 2 patient subgroups using pooled data from PIPF-004 and PIPF-006 (patient-level data from SP3 were unavailable). The first subgroup was patients with baseline FVC of 80% predicted or less. The manufacturer used a fixed-effects model to calculate standardised mean differences for change in per cent predicted FVC and 6-minute walk test distance and risk ratios for progression-free survival and mortality. The manufacturer indicated that there was a statistically significant treatment effect of 0.25 (95% CI 0.07 to 0.43, $p=0.007$) in change in per cent predicted FVC and a standardised mean difference of 0.25 (95% CI 0.07 to 0.44, $p=0.006$) in change in 6-minute walk test distance. The manufacturer noted substantial heterogeneity. Reduction in risk of death related to idiopathic pulmonary fibrosis (hazard ratio 0.42, 95% CI 0.21 to 0.84, $p=0.01$) and a trend to reduction in risk of all-cause mortality (hazard ratio 0.54, 95% CI 0.32 to 1.04, $p=0.07$) with treatment were also reported.

4.26 In its addendum, the manufacturer explained that there was a higher proportion of patients with obstructive disease in PIPF-006 compared with PIPF-004, and indicated that this could account for the difference in the FVC results between the 2 studies. The manufacturer presented results for a subgroup of patients with baseline FVC of 80% predicted or less who had borderline obstructive disease (see page 14 of the manufacturer’s
addendum). The manufacturer defined this as an FEV1/FVC ratio of less than 0.8. The manufacturer did not present meta-analysis results for the subgroup of patients with baseline FVC of 80% predicted or less excluding patients with borderline obstructive disease, which was the subgroup incorporated into its economic model, but advised that the 72-week hazard ratio for risk of mortality related to idiopathic pulmonary fibrosis was calculated as 0.25 (95% CI 0.10 to 0.63, p=0.003) using data from PIPF-004 and PIPF-006 and that this figure was incorporated into its updated economic model.

**Adverse effects of treatment**

4.27 The safety data in the manufacturer’s submission mainly related to a combined patient population from PIPF-004 and PIPF-006. Results for SP3, limited data for SP2 and interim results for PIPF-002 and PIPF-012 were also reported. A meta-analysis that combined selected safety data from the 3 phase III trials was provided.

4.28 The manufacturer advised that the safety of pirfenidone has been evaluated in clinical studies including 1345 healthy volunteers and patients. It noted that the most commonly reported (10% or greater) adverse effects with pirfenidone 2403 mg/day compared with placebo were nausea (32.8% compared with 13.3%), rash (28.7% compared with 8.6%), fatigue (22.3% compared with 13.3%), diarrhoea (21.7% compared with 13.5%), dyspepsia (16.8% compared with 5.5%), and photosensitivity reaction (12.2% compared with 1.7%). For full details of common treatment-emergent adverse effects in PIPF-004 and PIPF-006, see pages 153–155 of the manufacturer’s submission.

4.29 The manufacturer stated that discontinuation of therapy because of adverse effects was higher with pirfenidone 2403 mg/day than with
placebo (14.8% compared with 8.6%) in this population. In a meta-analysis of adverse effects that combined data from PIPF-004, PIPF-006 and SP3, the manufacturer reported that, compared with those receiving placebo, patients receiving pirfenidone were

4.30 The manufacturer reported that the interim analyses of the long-term PIPF-012 and PIPF-002 studies did not identify any new safety concerns. The manufacturer noted that the incidence of photosensitivity was lower in the PIPF-012 extension study than in the earlier PIPF-004 and PIPF-006 studies (19.7% compared with 44.4%). Furthermore, the incidence was lower in patients who had continued treatment with pirfenidone 2403 mg/day (12.3%) compared with those who had switched from placebo (28.1%).

Evidence Review Group comments

4.31 The ERG found that the manufacturer’s systematic review of the pirfenidone clinical studies was of acceptable quality and that it was unlikely that any relevant studies had been omitted. The ERG noted that it was unable to check statistical heterogeneity in the data presented in the meta-analyses because of the methods chosen by the manufacturer. The ERG advised that the manufacturer’s submission gave an unbiased estimate of pirfenidone’s efficacy at around 72 weeks. Furthermore, it found the manufacturer’s interpretation that pirfenidone seems to slow the rate of decline in lung function owing to idiopathic pulmonary
fibrosis was reasonable. The ERG did not perceive any significant safety concerns associated with the use of pirfenidone.

4.32 The ERG expressed concerns that the patient populations in the clinical trials may not be wholly representative of the population seen in secondary care in England and Wales. It noted that few patients in the trial had comorbidities that would normally be seen in clinical practice. The ERG added that many of the typical comorbidities could contribute to mortality and that this would not have been captured in the clinical trials (and especially during early follow-up of the studies). The ERG also noted that general severity of idiopathic pulmonary fibrosis (according to mean baseline FVC values of 73–81% across the 4 randomised controlled trials) was likely to be less severe in the trials than in UK clinical practice. However, the ERG indicated that there were limitations with the accuracy of FVC in measuring disease severity.

4.33 In its addendum, the ERG raised concerns about the manufacturer’s indirect comparison of pirfenidone and triple therapy. These included issues with the data from the PANTHER study and how these had been used. It noted that, according to clinical advice, the mortality rate for the placebo arm in the PANTHER study was low and that the prednisone doses used were higher than those used in UK clinical practice, which could have contributed to the observed outcomes. The ERG also described the following limitations associated with the indirect comparison of pirfenidone and triple therapy undertaken by the manufacturer:

- The lack of a summary of the PANTHER study data and their suitability for an indirect comparison.
• Minor differences in baseline patient characteristics between the PANTHER study and the pirfenidone trials (PIPF-004 and PIPF-006).

• Using all-cause mortality data from the PANTHER study and mortality related to idiopathic pulmonary fibrosis from PIPF-004 and PIPF-006.

• Basing the hazard ratio for the subgroup with FVC of 80% predicted or less on the whole group data from the PANTHER study compared with the subgroup data from the pirfenidone studies.

4.34 The ERG noted that the manufacturer’s submission did not specify treatment discontinuation owing to lack of response to pirfenidone. The ERG also advised that little was known about any impact of pirfenidone on acute exacerbations, dyspnoea, respiratory-related hospitalisation and quality of life.

*Intention-to-treat analyses*

4.35 The ERG found that the differences in efficacy between the pirfenidone 2403 mg/day and placebo groups were small and that these varied among the studies. It noted that although these differences generally favoured pirfenidone, they were not statistically significant in all cases. The ERG questioned the robustness of the categorical analysis of change in FVC and whether the absolute difference of 9% between the pirfenidone 2403 mg/day and placebo groups in patients with a decline in FVC of 10% or greater was statistically significant. The ERG stated that in its original report there appeared to be no clear reason why there were statistically significant differences between pirfenidone 2403 mg/day and placebo groups for many outcomes in PIPF-004 but not PIPF-006, but noted that the manufacturer provided a reasoned case in its addendum (see section 4.42).
4.36 The ERG noted that it was unclear if the differences in FVC between the pirfenidone 2403 mg/day and placebo groups were clinically significant. The ERG advised that a clinical specialist had confirmed that a decline in FVC of at least 10% in an individual patient was considered to be an accepted threshold for a clinically significant change. However, the ERG felt that a clinically significant effect in a cohort is likely to be lower. The ERG report cited recent research (which was sponsored by the manufacturer) that showed a decline in per cent predicted FVC of 5–10% had prognostic significance and that the minimally important clinical difference for a cohort with idiopathic pulmonary fibrosis was calculated as 2–6% of predicted normal values.

4.37 The ERG found that it was unclear if the differences in 6-minute walk test distances between the pirfenidone 2403 mg/day and placebo groups were clinically significant. The ERG indicated it had been advised by a clinical specialist that the pooled analysis result of a 24-metre difference between groups was on the threshold of clinical significance; however, the ERG stated that there is the potential for inadvertent bias when the test is administered.

4.38 The ERG noted uncertainties in the analyses of overall survival that were presented by the manufacturer. These included:

- how the results were calculated in relation to the different time points studied (that is, whether the data are being presented for up to 72 weeks or beyond 72 weeks)
- the absence of marked censored data on the graphs
- the lack of a description of the censoring methods
- the lack of information on distinguishing a treatment-emergent death that was related to idiopathic pulmonary fibrosis from one that was not
not knowing the follow-up period for the data

some inconsistencies in the hazard ratios (this may be because different time points were used but the ERG noted that this is not discussed in the manufacturer’s submission).

Subgroup analyses

4.39 The ERG highlighted uncertainties in the manufacturer’s original submission regarding the subgroup analysis of change in FVC according to baseline patient characteristics, and advised caution when interpreting the results:

- Although the results generally favoured pirfenidone 2403 mg/day, the confidence intervals were wide and often crossed the line of no effect, indicating that there was no treatment difference.
- It was unclear if the analysis was statistically significant and whether it was adequately powered.
- No data had been presented to support the manufacturer’s conclusion in its original submission that the analysis of a subgroup with baseline FVC of less than 80% predicted favoured pirfenidone 2403 mg/day.

4.40 The ERG reviewed the analysis of the subgroup of patients with baseline FVC of 80% predicted or less that was presented in the manufacturer’s addendum and noted a number of concerns:

- The ERG was unable to check the data in most cases.
- The FVC results were presented from the pooled analysis of PIPF-004 and PIPF-006 and results from the individual trials were not provided.
- No methods were presented by the manufacturer describing how the individual patient data were analysed.
- The analyses appeared to be post hoc and it was unclear if they were statistically powered to detect a difference between groups.
- Limited interpretation of the results was provided by the manufacturer.

4.41 The ERG advised that clinical specialists had indicated that a subgroup of people with FVC of 80% predicted or less was clinically plausible and would therefore be acceptable to patients and clinicians. However, it noted that some patients would be excluded, such as the small subset that has stable disease (and whose lung function does not deteriorate below the threshold) and those with co-existing emphysema.

4.42 The ERG reviewed the analysis of the subgroup with baseline FVC of 80% predicted or less excluding patients with borderline obstructive lung disease, and found that the manufacturer presented a reasoned case for the possibility that this contributed to the difference in efficacy between the PIPF-004 and PIPF-006 studies. The ERG queried the validity of the threshold chosen by the manufacturer, noting that NICE clinical guideline 101 stipulated a threshold of \( \text{FEV}_1/\text{FVC} <0.7 \). The ERG indicated that the manufacturer’s analysis was limited to the effect on per cent predicted FVC, and that the meta-analysis offered minimal statistical analysis and limited interpretation by the manufacturer. It was unable to check the data for this subgroup and recommended caution in interpreting the data because they appeared to be post hoc analyses and it was unclear if they were statistically powered to detect a difference between the 2 studies.

5 Comments from other consultees

5.1 The British Thoracic Society and the Royal College of Nursing advised that they were not aware of any current effective treatment
for this condition and indicated that best supportive care is used regularly in UK clinical practice. A clinical specialist and a patient expert advised that, if used, drug therapy directed at treating idiopathic pulmonary fibrosis usually comprises 1 or more drugs including prednisolone, azathioprine and N-acetylcysteine. The British Thoracic Society and a clinical specialist highlighted a recent interim analysis of the PANTHER study, which showed that patients receiving triple therapy (prednisolone, azathioprine and N-acetylcysteine) had worse outcomes than those receiving placebo. A patient expert noted the considerable adverse effects associated with long-term corticosteroid use, such as weight gain and impact on mood.

5.2 The professional groups noted significant geographical variation in current practice because patients are generally treated according to the clinical judgement of their physicians, with some offering best supportive care and others offering immunosuppressive therapy.

5.3 The British Thoracic Society advised that its guideline on interstitial lung disease was published before the results of the pirfenidone trials were available, but noted that the American Thoracic Society/European Respiratory Society 2011 consensus guideline does not routinely recommend pirfenidone for treating idiopathic pulmonary fibrosis.

5.4 The British Thoracic Society raised several areas of uncertainty in the clinical evidence for pirfenidone. Firstly, it stated the subgroup of patients recruited to the international clinical trials may not be representative of those diagnosed in the UK. Secondly, the definitions of disease severity used in the clinical trials may not necessarily reflect those patients with the poorest prognosis or those most likely to respond to therapy. It noted that potentially
toxic treatment should be targeted to patients whose disease is likely to progress rapidly and that there are scoring systems that might be applicable in this setting (although this have not been proven). Thirdly, it noted uncertainty associated with the surrogate end points used in the trials because, although there is good evidence that decline in FVC is correlated with mortality, it has not been proven that an intervention that reduces decline in FVC also reduces mortality.

5.5 The British Thoracic Society stated that the longitudinal change in lung function implied pirfenidone had a treatment effect, but noted that the primary end point was met in 1 phase III study (PIPF-004) and not in another (PIPF-006). The Royal College of Nursing noted that pirfenidone is relatively well tolerated; however, some patients may experience gastrointestinal disturbances when starting treatment. It further noted that some patients experience photosensitivity to sunlight, which can be severe. The British Thoracic Society noted that although pirfenidone does have significant adverse effects, the rate of treatment discontinuation was lower than several other large randomised controlled trials of treatments for idiopathic pulmonary fibrosis.

5.6 Uncertainty around the appropriate discontinuation of pirfenidone was raised by the British Thoracic Society. It explained that it is generally accepted that an acute exacerbation indicates disease progression, which might indicate lack of efficacy and justify discontinuation. Similarly, it was suggested that a decline in lung function (especially a decrease in VC of more than 10%) might also be considered as treatment failure. However, it noted that this may be harder to justify if the drug is well tolerated and the decline occurred a long time after starting therapy. It indicated that a fall in lung function together with a decline in functional status or
symptoms may be a reasonable trigger to stop therapy because symptoms, exercise capacity, quality of life and mortality are considered to be the most clinically important outcomes. A clinical specialist advised that there should be set criteria to assess whether the treatment is effective (for example, repeat lung function tests and 6-minute walk test) but that treatment should be continued for at least 24 weeks before deciding on discontinuation because of lack of efficacy.

5.7 The British Thoracic Society noted that it felt pirfenidone should be prescribed in secondary care by specialist multidisciplinary teams, but advised this could significantly impact on the organisation of care. All of the professional groups highlighted the necessity for a confirmed diagnosis of idiopathic pulmonary fibrosis before offering treatment with pirfenidone, noting that expert radiological or histological review may be needed. The Royal College of Nursing noted the need for monitoring of liver function and for known adverse effects (for example, photosensitivity, rash and nausea) and felt that this could be performed by a specialist nurse. It was stated that pirfenidone is currently only available at selected centres on a named patient basis.

6 Cost-effectiveness evidence

6.1 The manufacturer was unable to identify any published cost-effectiveness studies that were relevant to the decision problem. In its original submission, the manufacturer submitted a de novo model that evaluated the cost effectiveness of pirfenidone compared with best supportive care in patients with mild to moderate idiopathic pulmonary fibrosis, which is consistent with its UK marketing authorisation. The base case included the total pooled patient population for PIPF-004 and PIPF-006 and a
subgroup analysis investigated the patients with baseline FVC of 80% predicted or less. The analysis was conducted from an NHS and personal and social services perspective. A lifetime horizon (60 years) was used and a 3.5% discount rate was adopted for health benefits and costs.

6.2 In its addendum, the manufacturer updated its model so that it evaluated pirfenidone against 2 additional comparators: triple therapy and a pooled comparator. The pooled comparator analysis was based on the manufacturer’s prediction of relative use of triple therapy and best supportive care in the UK over the next 5 years. The manufacturer achieved this by combining the existing outputs of the model, best supportive care and triple therapy, rather than incorporating a third comparator into the Visual Basic for Applications code (see appendix 6 of the manufacturer’s addendum).

6.3 The manufacturer advised that it had made further changes to the model in its addendum:

- Discontinuation rates had been updated using new data from the PIPF-012 extension study from 72 weeks up to 192 weeks (that is, following on from data from PIPF-004 and PIPF-006 for up to 72 weeks).
- A miscalculation regarding the average number of pirfenidone pills had been corrected.
- An additional subgroup had been modelled; patients with baseline FVC of 80% predicted or less excluding patients with borderline obstructive disease (defined as an FEV₁/FVC ratio of less than 0.8).

6.4 An overview of the manufacturer’s economic model, which used a Markov-type structure, is presented in figure 1.
The manufacturer’s micro-simulation model sampled 24-week changes in FVC and the 6-minute walk test distance in each cycle to capture treatment effect and estimated the risk of death related to idiopathic pulmonary fibrosis, risk of all-cause hospitalisation and quality of life (using St George’s Respiratory Questionnaire scores). Because there were limited deaths in the PIPF-004 and PIPF-006 studies, the manufacturer incorporated data from GIPF-007 (a study comparing interferon-gamma with placebo but with a similar study design to PIPF-004 and PIPF-006), which enabled more precise survival estimates to be generated for the best supportive care group over a longer time horizon. The manufacturer explained that at the end of each cycle, the patient’s age, gender, FVC and 6-minute walk test distance were used to predict the probability of transitioning into one of 6 health states:

- dead owing to causes related to idiopathic pulmonary fibrosis (hospitalised)
- dead owing to causes unrelated to idiopathic pulmonary fibrosis (hospitalised)
- dead owing to causes related to idiopathic pulmonary fibrosis (not hospitalised)
• dead owing to causes unrelated to idiopathic pulmonary fibrosis (not hospitalised)
• alive (hospitalised)
• alive (not hospitalised).

Surviving patients accumulated quality-adjusted life years (QALYs) and continued to the next cycle while patients who died exited the model.

6.5 The manufacturer outlined how the transition probabilities were calculated from the clinical data for any given 24-week cycle. Probability of mortality related to idiopathic pulmonary fibrosis was based on a regression analysis that used FVC and 6-minute walk test distance as independent variables. For pirfenidone compared with best supportive care, this was calibrated to the 72-week hazard ratio and mortality rates from the PIPF-004 and PIPF-006 trials. For pirfenidone compared with triple therapy, it was calibrated to the indirect hazard ratio that was derived from the mortality related to idiopathic pulmonary fibrosis at 72 weeks in PIPF-004 and PIPF-006 and the all-cause mortality at 60 weeks in the PANTHER study (see section 4.21). The manufacturer found that overall survival was predicted well and felt that the median survival for the best supportive care group was clinically realistic at 4.8 years. The probability of mortality unrelated to idiopathic pulmonary fibrosis was based on all-cause mortality rates for the UK population. Probability of hospitalisation was also based on a regression analysis that used FVC and 6-minute walk test distance as independent variables.

Utility values

6.6 The manufacturer conducted a systematic literature review for studies on health-related quality of life and identified 20 relevant
studies. The manufacturer reported that St George’s Respiratory Questionnaire scores and the World Health Organization Quality-of-life Questionnaire scores in the literature were similar to those seen in the pirfenidone clinical trials (PIPF-004 and PIPF-006).

6.7 The manufacturer explained because the quality-of-life data from the pirfenidone clinical trials were only available up to 72 weeks, the utility values used in its economic model were estimated by mapping the St George’s Respiratory Questionnaire scores predicted by the model onto the EQ-5D. The St George’s Respiratory Questionnaire scores were estimated by linear regression using FVC and the 6-minute walking test distance as independent variables. No disutilities for adverse effects were incorporated by the manufacturer because it was assumed that adverse effects would not markedly affect quality of life. The manufacturer did not report how the utility values for triple therapy were derived.

Costs

6.8 The manufacturer was unable to identify any relevant studies regarding resource use and costing for idiopathic pulmonary fibrosis in the UK. The manufacturer included treatment-associated costs and health state costs in its economic model. The treatment-associated costs for each cycle for the pirfenidone group comprised the cost of the technology plus oxygen and monitoring costs (£884.92 for the first cycle then £800.17 for subsequent cycles). Only oxygen and monitoring costs were applied to the best supportive care group. The costs for pirfenidone were supplied by the manufacturer because a list price
had not yet been confirmed. The manufacturer stated that the annual total costs for triple therapy were £302.38, based on prices in the latest ‘Monthly Index of Medical Specialities’ (prednisolone and azathioprine) or expert opinion (N-acetylcysteine). The treatment-associated costs for each cycle for the triple therapy group were £94 in the first cycle, £90 in the second cycle and £84 in the third and subsequent cycles (these costs were extracted from the manufacturer’s updated model). The oxygen and monitoring costs were taken from NHS reference costs (2009/10), ‘Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis’ (NICE technology appraisal guidance 199) and the Regional Drugs and Therapeutic Centre.

6.9 Costs for each of the 6 health states for the cohorts receiving pirfenidone or best supportive care were provided in the manufacturer’s original submission (table 6). These were calculated by the manufacturer by adding, as appropriate, costs for treatment, oxygen and monitoring, hospitalisation and end-of-life costs (which depended on whether death was related to idiopathic pulmonary fibrosis or not). In its addendum, the manufacturer advised that total costs for the pooled comparator comprised the same parameters (numbers not provided); total costs for triple therapy were not described. Hospitalisation costs were based on Personal Social Services Research Unit data, and the manufacturer stated that these were lower for pirfenidone to reflect the shorter mean stay that was observed with pirfenidone in the clinical trials. End-of-life costs were based on a report from the National Audit Office (2008) and inflated to 2011 prices. The manufacturer stated that NHS reference costs (2009/10) were used whenever possible.
Table 6 Health state costs in manufacturer’s economic model\textsuperscript{a}

<table>
<thead>
<tr>
<th>Health State</th>
<th>Pirfenidone</th>
<th>Best supportive care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death related to idiopathic pulmonary fibrosis, not hospitalised</td>
<td></td>
<td>£21,886</td>
</tr>
<tr>
<td>Death not related to idiopathic pulmonary fibrosis, not hospitalised</td>
<td></td>
<td>£16,792</td>
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<tr>
<td>Death related to idiopathic pulmonary fibrosis, hospitalised</td>
<td></td>
<td>£24,456</td>
</tr>
<tr>
<td>Death not related to idiopathic pulmonary fibrosis, hospitalised</td>
<td></td>
<td>£19,362</td>
</tr>
<tr>
<td>Alive, hospitalised</td>
<td></td>
<td>£3,370</td>
</tr>
<tr>
<td>Alive, not hospitalised</td>
<td></td>
<td>£800</td>
</tr>
</tbody>
</table>

\textsuperscript{a} These costs are applicable from cycle 4 onwards. Costs for earlier cycles were higher because of additional costs for oxygen (best supportive care and pirfenidone) and treatment (pirfenidone only).

Source: Manufacturer’s original submission, page 228

The manufacturer advised that costs for managing treatment-associated adverse effects of pirfenidone were not included because managing these would not typically attract significant costs. It noted that any substantial cost consequences would be captured during hospitalisation. The manufacturer did not discuss in its addendum how any costs of managing treatment-associated adverse effects of triple therapy would be captured by the model.

Results

6.10 The manufacturer compared clinical outcomes using the economic model with the results from the clinical trials (PIPF-004 and PIPF-006). It found that the model exactly replicated the clinical trial data for 72-week mortality related to idiopathic pulmonary fibrosis for best supportive care (7.2%) and pirfenidone (3.9%) and the hazard ratio for mortality related to idiopathic pulmonary fibrosis (0.53). The manufacturer stated that it anticipated that the hazard ratio was unchanged after updating the model with longer-term continuation data from PIPF-012. The manufacturer highlighted that mortality unrelated to idiopathic pulmonary fibrosis was higher in the model than in the clinical trials for best supportive care (2.5%
compared with 1.7%) and pirfenidone (2.5% compared with 2.3%). It explained that this reflected clinical practice because patients with comorbidities had been excluded from PIPF-004 and PIPF-006. The manufacturer also noted that the model underpredicted the change in quality of life with best supportive care (change in St George’s Respiratory Questionnaire score compared with 1.7%) and with pirfenidone compared with 2.5%). However, because the relative difference and absolute value were fairly similar, the manufacturer felt that the model results would not be greatly affected. The manufacturer did not discuss in its addendum how well the model predicted quality of life with triple therapy.

6.11 For the population with mild to moderate disease, the manufacturer presented base-case analyses for pirfenidone compared with best supportive care, triple therapy and the pooled comparator using the updated economic model supplied with its addendum (table 7). The manufacturer’s results showed that treating idiopathic pulmonary fibrosis using pirfenidone increased the cost of treatment but was associated with more QALYs than any of the comparators. The manufacturer’s incremental cost-effectiveness ratios (ICERs) for pirfenidone compared with its comparators were compared with best supportive care, compared with triple therapy and compared with the pooled comparator in the population with mild to moderate disease. In the model supplied with the original submission, the manufacturer’s ICER for pirfenidone compared with best supportive care was (incremental costs ; incremental QALYs ).
Table 7 Manufacturer's base-case results: mild to moderate population (updated economic model)

<table>
<thead>
<tr>
<th></th>
<th>Total costs</th>
<th>Total QALYs</th>
<th>Incremental costs versus pirfenidone</th>
<th>Incremental QALYs versus pirfenidone</th>
<th>ICER (pirfenidone versus comparator)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pirfenidone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best supportive care</td>
<td>£36,370</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triple therapy</td>
<td>£24,711</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled comparator</td>
<td>£34,673</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Source: Manufacturer’s addendum, page 24

6.12 For the population with baseline FVC of 80% predicted or less, the manufacturer presented subgroup analyses for pirfenidone compared with best supportive care, triple therapy and the pooled comparator using the updated economic model supplied with its addendum (table 8). The manufacturer’s results show that treating idiopathic pulmonary fibrosis using pirfenidone increased the cost of treatment but was associated with more QALYs than best supportive care, triple therapy or the pooled comparator. The manufacturer’s incremental cost-effectiveness ratios (ICERs) for pirfenidone were compared with best supportive care, compared with triple therapy and compared with the pooled comparator in the population with baseline FVC of 80% predicted or less. In the model supplied with the original submission, the manufacturer’s ICER for pirfenidone compared with best supportive care was (incremental costs; incremental QALYs).
When patients with borderline obstructive disease (defined as an FEV₁/FVC ratio of less than 0.8) were excluded, the manufacturer’s ICERs were:

- **for pirfenidone compared with best supportive care (incremental costs ; incremental QALYs )**
- **for pirfenidone compared with triple therapy (incremental costs ; incremental QALYs )**
- **for pirfenidone compared with the pooled comparator (incremental costs ; incremental QALYs ).**

6.13 The manufacturer undertook a probabilistic sensitivity analysis of the updated economic model provided with the addendum to explore uncertainty around the cost-effectiveness results. It indicated that the probability of pirfenidone being cost effective at £30,000 per QALY gained in the population with mild to moderate disease was compared with best supportive care and compared with triple therapy. For the population with baseline FVC
of 80% predicted or less, the manufacturer stated that there was a □ probability that pirfenidone was cost effective at £30,000 per QALY gained compared with triple therapy and □ probability compared with best supportive care.

6.14 Univariate sensitivity analyses were performed by the manufacturer to test the robustness of the updated model provided with its addendum using the population with baseline FVC of 80% predicted or less (see page 42–44 of the manufacturer’s addendum for the full range). The manufacturer reported that the ICERs were sensitive to changes in the discount rates for costs and health outcomes, the number of pills taken each day and the adjustment factors used to replicate mortality related to idiopathic pulmonary fibrosis in PIPF-004 and PIPF-006. The comparison of pirfenidone with best supportive care is shown in table 9 and with triple therapy in table 10. Sensitivity analyses using the mild to moderate population in the updated model were not described by the manufacturer; sensitivity analyses for this population using the original model are presented on pages 237–8 of the manufacturer’s original submission.
Table 9 Manufacturer's univariate sensitivity analyses for pirfenidone compared with best supportive care (updated economic model): key factors

<table>
<thead>
<tr>
<th>Parameter value</th>
<th>Incremental cost (£)</th>
<th>Incremental QALYs</th>
<th>ICER (£ per QALY gain)</th>
<th>Difference from base case (£ per QALY gain)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base case</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discount rate for costs 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>6%</td>
<td></td>
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<tr>
<td>Discount rate for outcomes 0%</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>6%</td>
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<td></td>
</tr>
<tr>
<td>Pills per day</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSC adjustment factor +25%</td>
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<tr>
<td></td>
<td>−25%</td>
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<td></td>
<td></td>
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<tr>
<td>Pirfenidone adjustment factor +25%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>−25%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year
Source: Manufacturer's addendum, page 42–3
Table 10 Manufacturer’s univariate sensitivity analyses for pirfenidone compared with triple therapy (updated economic model): key factors

<table>
<thead>
<tr>
<th>Parameter value</th>
<th>Incremental cost (£)</th>
<th>Incremental QALYs</th>
<th>ICER (£ per QALY gain)</th>
<th>Difference from base case (£ per QALY gain)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
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<td>***</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>Discount rate for costs 0%</td>
<td>***</td>
<td>***</td>
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<tr>
<td>6%</td>
<td>***</td>
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<tr>
<td>Discount rate for outcomes 0%</td>
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</tr>
<tr>
<td>6%</td>
<td>***</td>
<td>***</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>Pills per day 3</td>
<td>***</td>
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<td>***</td>
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</tr>
<tr>
<td>9</td>
<td>***</td>
<td>***</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>TT adjustment factor +25%</td>
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<td>***</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>-25%</td>
<td>***</td>
<td>***</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>Pirfenidone adjustment factor +25%</td>
<td>***</td>
<td>***</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>-25%</td>
<td>***</td>
<td>***</td>
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<td>***</td>
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</tbody>
</table>

Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TT, triple therapy
Source: Manufacturer’s addendum, page 43–4

Evidence Review Group comments

6.15 The ERG found that the manufacturer’s cost-effectiveness analysis met the requirements of the NICE reference case and was generally appropriate. However, it noted that although the manufacturer’s economic model was presented in Excel, it had been coded as an individual patient simulation in Visual Basic for Applications, which made it less accessible and more difficult to critique and interpret.
6.16 The ERG found the changes to the manufacturer’s original model to be reasonable, including the updated discontinuation rates and increased patient numbers in the sampled population, as was the assumption that the mortality rate did not change, and noted a small impact on the ICER. The ERG verified that the results obtained with the manufacturer’s updated model were consistent with the original version but was unable to check data for the discontinuation rates or pills per day.

6.17 The ERG noted that the mild to moderate population in the manufacturer’s economic model was from relevant trials, but that this may not be wholly representative of patients treated in clinical practice in the UK because the trial population may have had milder idiopathic pulmonary fibrosis.

6.18 The ERG advised that best supportive care (rather than active treatment) is routinely used in the UK and consequently this was an appropriate comparator in the manufacturer’s original and updated economic models.

6.19 The ERG critiqued the inclusion of triple therapy in the manufacturer’s updated economic model. In its original report, the ERG agreed with the manufacturer’s finding that there were no suitable randomised controlled trials to enable an indirect comparison with triple therapy at the time of its original submission. In its addendum, the ERG cited concerns about the reliability of the subsequent comparison of pirfenidone and triple therapy that was presented in the manufacturer’s addendum. The concerns included uncertainty in the discontinuation rates taken from the PANTHER study and weaknesses in the data used for the indirect comparison (see section 4.33). In addition to the issues with the clinical data, the ERG had further concerns about how the data had been
incorporated into the manufacturer’s updated economic model after checking the results from the analyses for triple therapy. The ERG noted that the manufacturer’s model results predicted that about [number] of patients with mild to moderate disease who are being treated with triple therapy will die within 6 months. The ERG indicated that this was inconsistent with the PANTHER study, in which about 11% of patients in the triple-therapy arm died in this time period. Furthermore, the ERG noted that the analyses for the subgroups with FVC of 80% predicted or less assumed an even higher mortality rate for the triple-therapy group (die within 6 months). The ERG noted that total costs for triple therapy in the manufacturer’s model were less than for best supportive care (because reduced overall survival is associated with lower hospitalisation costs) and agreed that these costs reasonably reflected the model’s assumptions. However, given the inconsistency between the survival rates in the PANTHER study and those used in the manufacturer’s updated model, the ERG concluded that the analyses presented by the manufacturer for triple therapy were flawed.

6.20 The ERG reviewed the inclusion of the pooled comparator, which was based on the manufacturer’s prediction of relative use of triple therapy and best supportive care in the UK over the next 5 years. The ERG considered that the manufacturer’s assumptions for the current use and future decline appeared reasonable, although clinical advice to the ERG suggested that the use of triple therapy in current practice varies widely. However, the ERG expressed concerns about the relevance of the pooled comparator to the appraisal, noting that it was not specified in the decision problem. It explained that in a fully incremental analysis, interventions are considered to be mutually exclusive, meaning that adopting one intervention excludes all others and consequently all patients
receive the same treatment. It further commented that a fully incremental analysis allows the most cost-effective intervention to be identified, providing useful information for decision-making when assessing health technologies. The ERG therefore recommended that results should be interpreted using the fully incremental analyses for the comparators in the decision problem, rather than results using the pooled comparator.

6.21 The ERG noted that not all model parameters had been included in the univariate or probabilistic sensitivity analyses in the manufacturer’s original and updated models, including key parameters associated with overall survival, hospitalisations and quality of life. It advised that consequently the full uncertainty around the model results had not been shown.

6.22 The ERG found that probabilistic sensitivity analyses using the manufacturer’s updated model showed that, at £30,000 per QALY gained, there was [missing text] of pirfenidone compared with best supportive care in the mild to moderate population, the subgroup of patients with FVC of 80% predicted or less, and the subgroup of patients with FVC of 80% predicted or less excluding patients with borderline obstructive disease.

6.23 The ERG noted uncertainty around the cost-effectiveness analysis of the subgroup of patients with FVC of 80% predicted or less, and the subgroup of patients with FVC of 80% predicted or less excluding patients with borderline obstructive disease. It observed that although the manufacturer’s approach in estimating mortality related to idiopathic pulmonary fibrosis seemed sound, limited detail had been provided, and these were post hoc analyses. The
ERG concluded that the results for the subgroups should be considered cautiously.

**ERG additional analyses**

6.24 The ERG conducted several additional analyses using the manufacturer’s original model to explore uncertainty around the regression coefficients used to estimate treatment effect, mortality related to idiopathic pulmonary fibrosis, quality of life and length of hospital stay.

6.25 The ERG noted that the regression coefficients that were used in the manufacturer’s original model to estimate survival, hospitalisation and quality of life had not been subject to sensitivity analyses. The ERG explored the impact of varying these regression coefficients by running the original model using the upper and lower confidence interval estimates for each one. It found that the ICER varied from *, which is a wider range than that reported by the manufacturer in its scenario analyses. When the model was run using the upper limit of all coefficients for the relevant regression equations, the ERG found that the ICER dropped to **.

6.26 The ERG analysed the impact of using the upper and lower limits of the 95% confidence interval for the hazard ratio at 72 weeks for mortality related to idiopathic pulmonary fibrosis (hazard ratio 0.53, 95% CI 0.288 to 1.028). At the lower limit of the 95% confidence interval, the ERG noted that the ICER decreased to *** for pirfenidone compared with best supportive care. When the upper limit was used, the ERG found that the ICER increased to ****
6.27 The ERG found that the ICER was highly sensitive to changes in patients’ quality of life. Patients’ quality of life was over- and under-estimated using the limits of the 95% confidence interval for the St George’s Respiratory Questionnaire coefficients and the EQ-5D coefficients. Using the manufacturer’s original model, overestimating quality of life decreased the ICER for pirfenidone compared with best supportive care; underestimating it increased the ICER.

6.28 The ERG found that assuming the same length of hospital stay in the pirfenidone and best supportive care arms had little impact on the ICER.

7 End-of-life considerations

7.1 The manufacturer summarised the potential eligibility of pirfenidone for consideration under the end-of-life criteria in its addendum, which was critiqued by the ERG.

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Data available</th>
</tr>
</thead>
<tbody>
<tr>
<td>The treatment is indicated for patients with a short life expectancy, normally less than 24 months</td>
<td>The manufacturer indicated that although the predicted mean survival was 4 years for the subgroup with baseline FVC of 80% predicted or less treated with best supportive care, idiopathic pulmonary fibrosis is a very heterogeneous disease and some patients will die within a year (Ley, 2011). A viewpoint published recently in the Lancet noted that the incidence of acute exacerbations and death during the first 48–72 weeks of most clinical trials is low (roughly 10–15%) in patients with mild to moderate idiopathic pulmonary fibrosis, and gave a disease duration of less than 4–5 years after diagnosis (Raghu, 2012).</td>
</tr>
</tbody>
</table>

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Median survival for the overall population with idiopathic fibrosis has been estimated at 2–5 years from diagnosis (Meltzer and Noble, 2008). The ERG noted that it had received clinical advice that confirmed the median life expectancy for patients with idiopathic pulmonary fibrosis is greater than 2 years.

There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment. The manufacturer highlighted the results of an independent meta-analysis of treatments for idiopathic fibrosis, which showed pirfenidone delays disease progression by 30% (Spagnolo, 2010).

The manufacturer advised that the economic modelling estimated that approximately 💼 were gained with pirfenidone in the population with mild to moderate idiopathic pulmonary fibrosis.

The treatment is licensed or otherwise indicated for small patient populations. The manufacturer stated that it had estimated that 10,000–13,000 people in England and Wales have idiopathic pulmonary fibrosis (Orphannet, 2011; Navaratnam et al., 2011). Pirfenidone has a marketing authorisation for the treatment of ‘mild to moderate’ disease. It acknowledged that there is no consensus on defining this term, but noted that a French cohort study found that 70% of patients with idiopathic pulmonary fibrosis had mild to moderate disease, defined as FVC greater than 50% predicted and DLco greater than 35% predicted (Data on file, InterMune). If the same criteria are applied to the figures provided by the manufacturer for England and Wales, this produces an estimated population of 7000–9100 covered by the marketing authorisation.

8 Equalities issues

8.1 Assessment and treatment of idiopathic pulmonary fibrosis varies because of a lack of regional specialist centres and the absence of clearly defined care pathways. Consequently, unless delivery of a

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new treatment is coordinated through specialist centres, it is possible that it will not be equitable across different geographical regions. Idiopathic pulmonary fibrosis is more common in men of low socioeconomic status and those who work in certain jobs.

9  **Innovation**

9.1 The manufacturer stated that pirfenidone is the first drug for idiopathic pulmonary fibrosis that has shown clinically relevant and consistent benefits across several outcome variables including lung function, exercise capacity, progression of disease and mortality. The European public assessment report for pirfenidone noted that idiopathic pulmonary fibrosis is typically refractory to existing treatments and that the diagnosis would likely be re-evaluated in the event of a response, concluding: ‘In these circumstances it is remarkable to have 4 studies showing a beneficial effect on the rate of decline of pulmonary function’.

9.2 The manufacturer explained that introducing pirfenidone as a treatment option for idiopathic pulmonary fibrosis would trigger activities that would ultimately deliver health benefits that would not be captured in the QALY calculation. It suggested these would include the development of clinical guidelines to improve quality and consistency of care, physician education and patient support and avoid the use of unlicensed or off-label treatments that have no evidence base for their use.

9.3 The ERG received advice from clinical specialists that pirfenidone is one of several therapies targeting new pathways in idiopathic pulmonary fibrosis. It noted that this represented a step-wise change from previous models of drug development and can be seen as innovative, and added that the suggestions made by the
manufacturer would broadly improve patient care because palliative care for people with idiopathic pulmonary fibrosis is lacking.

10 Authors

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Bhash Naidoo
Technical Adviser

with input from the Lead Team (Matt Bradley, Ian Campbell and Paddy Storrie).
Appendix A: Supporting evidence

Related NICE guidance

Under development
NICE is developing the following guidance (details available from www.nice.org.uk):

- Idiopathic pulmonary fibrosis: the diagnosis and management of suspected idiopathic pulmonary fibrosis. NICE clinical guideline (publication expected June 2013).