Pirfenidone for treating idiopathic pulmonary fibrosis

Technology appraisal guidance
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## Contents

1 Guidance ............................................................................................................................................................................ 4
2 The technology ............................................................................................................................................................... 5
3 The manufacturer's submission ........................................................................................................................................ 6
   Clinical effectiveness .......................................................................................................................................................... 6
   Cost effectiveness ............................................................................................................................................................ 17
   Evidence Review Group comments .............................................................................................................................. 23
4 Consideration of the evidence .......................................................................................................................................... 31
   Summary of Appraisal Committee's key conclusions ..................................................................................................... 43
5 Implementation ................................................................................................................................................................. 52
6 Recommendations for further research .......................................................................................................................... 53
7 Related NICE guidance .................................................................................................................................................... 54
   Under development ......................................................................................................................................................... 54
8 Review of guidance ............................................................................................................................................................ 55
9 Appraisal Committee members, guideline representatives and NICE project team ................................................. 56
   A Appraisal Committee members .................................................................................................................................... 56
   B Guideline representatives .............................................................................................................................................. 59
   C NICE project team ....................................................................................................................................................... 59
10 Sources of evidence considered by the Committee ........................................................................................................ 60
   About this guidance .......................................................................................................................................................... 62
1 Guidance

1.1 Pirfenidone is recommended as an option for treating idiopathic pulmonary fibrosis only if:

- the person has a forced vital capacity (FVC) between 50% and 80% predicted and
- the manufacturer provides pirfenidone with the discount agreed in the patient access scheme.

1.2 Treatment with pirfenidone that is recommended according to 1.1 should be discontinued if there is evidence of disease progression (a decline in per cent predicted FVC of 10% or more within any 12 month period).

1.3 People currently receiving pirfenidone that is not recommended according to 1.1 should have the option to continue treatment until they and their clinician consider it appropriate to stop.
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 and platelet-derived growth factor. 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 (costs from manufacturer's submission; 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. The manufacturer of pirfenidone has agreed a patient access scheme with the Department of Health that makes pirfenidone available with a discount. The size of the discount is commercial in confidence (see section 5.3). The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.
3 The manufacturer’s submission

The Appraisal Committee (section 9) considered evidence submitted by the manufacturer of pirfenidone and a review of this submission by the Evidence Review Group (ERG; section 10).

**Clinical effectiveness**

3.1 The manufacturer presented 4 randomised studies in its submission, PIPF-004, PIPF-006 and SP3 and SP2. Another 2 studies were excluded (the reason for this is confidential). Of 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, also known as RECAP, which is an extension of PIPF-004 and PIPF-006 and is expected to complete in 2015) and a safety study (PIPF-002).

3.2 PIPF-004 and PIPF-006 (also known as CAPACITY-2 and CAPACITY-1 respectively) 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 diffusing capacity of the lung for carbon monoxide [DLCO] 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). Both trials were conducted in Australia, Europe and North America. 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.

3.3 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.
In an ongoing non-controlled long-term study (PIPF-002), patients (n=83) received pirfenidone at a dosage of up to 3600 mg/day.

### 3.4 The primary outcomes of the studies were:

- Baseline-to-end point change in per cent predicted FVC (PIPF-004 and PIPF-006) or vital capacity (VC; SP3 study);
- Change in supplemental oxygen use (SpO₂) 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 change in 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 SpO₂ 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. A pre-planned pooled analysis used the intention-to-treat pooled population of PIPF-004 and PIPF-006. From PIPF-004, only the results using the licensed dosage of pirfenidone (2403 mg/day) are summarised here.

### Intention-to-treat analyses

#### 3.5 The manufacturer presented results for change in per cent predicted FVC for the pirfenidone 2403 mg/day and placebo groups from PIPF-004, PIPF-006 and a pooled analysis of the 2 studies. There was a statistically significant difference in the mean decline in per cent predicted FVC at 72 weeks in favour of pirfenidone in PIPF-004 (−8.0% compared with −12.4%, p=0.001) and in the pooled analysis (−8.5% compared with −11.0%, p=0.005), but not in PIPF-006 (−9.0% compared with −9.6%, p=0.501). The Food and Drug Administration (FDA) briefing for the Pulmonary Advisory Committee reported that the absolute difference between the pirfenidone 2403 mg/day and placebo groups in median FVC decline was 1.1% in both PIPF-004 and PIPF-006.

#### 3.6 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 SpO₂ in the 6-minute walk test, per cent predicted DL\textsubscript{CO}, dyspnoea and time to worsening of idiopathic pulmonary fibrosis. For categorical change in per cent predicted FVC at week 72, the manufacturer stated that in PIPF-004 a lower proportion of patients in the pirfenidone 2403 mg/day group experienced a decline of 10% or
higher compared with the placebo group, which was statistically significant (20.1% and 34.5%, p=0.001), and similar results were presented in a pooled analysis of PIPF-004 and PIPF-006 (21% compared with 31%, p=0.003). However, there was no statistically significant difference between pirfenidone and placebo groups in PIPF-006 (23% compared with 27%, p=0.440). The manufacturer's 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, p=0.171); however, there was a statistically significant difference between the groups in PIPF-006 (absolute difference of 31.8 metres, p<0.001) and in the pooled analysis (absolute difference of 24.0 metres, p<0.001). The manufacturer noted that the minimal clinically important difference has been estimated at 24–45 metres and 28 metres in 2 recent studies.

3.7 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 DL_{CO}, or death. There was a statistically significant reduction in the risk of death or disease progression with pirfenidone 2403 mg/day compared with placebo in PIPF-004 (hazard ratio 0.64 [95% CI 0.44 to 0.95], p=0.0235) and in the pooled analysis (hazard ratio 0.74 [95% CI 0.57 to 0.96], p=0.025) but not in PIPF-006 (hazard ratio 0.84 [95% CI 0.58 to 1.22], p=0.355).

3.8 Less than 10% of patients died in PIPF-004 and PIPF-006. The manufacturer presented an exploratory analysis of overall survival for all patients. 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). In another exploratory analysis, the manufacturer reported that the incidence of idiopathic pulmonary fibrosis-related deaths was lower in the pirfenidone 2403 mg/day group than in the placebo group (12 compared with 25 deaths in the pooled analyses; hazard ratio 0.62 [95% CI, 0.35 to 1.13]). The timeframe for this analysis was not stated by the manufacturer and it is not clear how this differs from the published analysis (Noble et al. 2011), which reported idiopathic pulmonary fibrosis-related mortality rates of 5% in the
pirfenidone 2403 mg/day group compared with 8% in the placebo group (18 and 28 deaths respectively; hazard ratio 0.62 [95% CI 0.35 to 1.13], p=0.117) for death at any time within the study duration (mean length of follow-up was not reported). The manufacturer estimated the mortality rates at 72 weeks (the time point for the primary outcome) to be 3.9% for pirfenidone and 7.2% for placebo. It calculated that the hazard ratio for mortality related to idiopathic pulmonary fibrosis up to 72 weeks was 0.53 (95% CI 0.288 to 1.028, p=0.0606). Because of lower patient numbers for follow-up after 72 weeks, the manufacturer considered this hazard ratio at 72 weeks to be the most robust in calculating pirfenidone’s overall treatment effect and implemented it in its economic model.

3.9 The manufacturer described a further exploratory 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 was 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 for pirfenidone compared with placebo was noted in the manufacturer’s pooled analysis (hazard ratio 0.48 [95% CI 0.24 to 0.95], p=0.030) but not in the individual studies PIPF-004 (hazard ratio 0.45 [95% CI 0.16 to 1.30], p=0.129) and PIPF-006 (hazard ratio 0.50 [95% CI 0.20 to 1.23], p=0.121).

3.10 In response to consultation, the manufacturer provided further information about the reporting of the overall survival analyses. It clarified the classification of deaths from pneumonia in PIPF-004 and PIPF-006. It also described the follow-up period and the censoring methods and provided graphs with marked censored data.

3.11 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, measured using the World Health Organization Quality-of-life
Questionnaire or by change in respiratory status. The results of these analyses are confidential.

3.12 The manufacturer stated that no respiratory instrument specific to idiopathic pulmonary fibrosis was available when the study started, so respiratory status was measured using the St George's Respiratory Questionnaire, which 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 pooled intention-to-treat population of PIPF-004 and PIPF-006. The results of these analyses are confidential.

3.13 The manufacturer provided a post-hoc analysis of hospitalisation in PIPF-004 and PIPF-006 that showed a similar number of hospitalisations for respiratory and non-respiratory reasons for patients receiving pirfenidone 2403 mg/day (123 out of 345 patients had at least 1 hospitalisation) and patients receiving placebo (108 out of 347 patients had at least 1 hospitalisation). However, it reported that the mean duration of stay in hospital was lower for the pirfenidone group than for the placebo group for respiratory-related reasons (8.0 days compared with 14.6 days) and non-respiratory reasons (8.8 days compared with 18.0 days).

3.14 In the SP3 study, treatment with pirfenidone 1800 mg/day was associated with a statistically significant 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 pirfenidone 1200 mg and 1800 mg/day groups. The manufacturer's analysis of progression-free survival showed that pirfenidone 1800 mg/day statistically 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.

3.15 In the SP2 study, 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 statistically significant difference favouring pirfenidone between the 2 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.

3.16 In response to consultation, the manufacturer provided further data from PIPF-012. These included Kaplan–Meier plots for the subgroup with baseline FVC 80% predicted or less that showed the number at risk of death from week 0 (at the start of PIPF-004 and PIPF-006) up to 192 weeks. At week 0, there were 244 patients taking pirfenidone in PIPF-004 and PIPF-006, and 233 patients taking placebo. The manufacturer also presented analyses of 178 patients who had switched to pirfenidone in PIPF-012 after receiving placebo in PIPF-004 or PIPF-006 and who had baseline values that met the entry criteria for PIPF-004 and PIPF-006. The mean change from baseline to week 60 in per cent predicted FVC was −5.8% for the patients who had switched from placebo to pirfenidone in PIPF-012 compared with −7.0% in the pirfenidone group (n=345) and −9.4% in the placebo group (n=347) in PIPF-004 and PIPF-006. The percentage of patients with an FVC decline 10% or more was 16.3% in PIPF-012 compared with 16.8% in the pirfenidone group and 24.8% in the placebo group in PIPF-004 and PIPF-006. The manufacturer stated that overall survival in newly treated patients in PIPF-012 was similar to that of patients taking pirfenidone in PIPF-004 and PIPF-006 (numbers not provided).

3.17 In response to consultation and to demonstrate the generalisability of the trial populations to the UK clinical population, the manufacturer provided early findings from a multicentre, retrospective, cohort review that is investigating clinical experience with pirfenidone in routine UK clinical practice across 4 NHS trusts through a named patient programme. Mean baseline values for a cohort of 106 patients treated with pirfenidone in the named patient programme were lower than in PIPF-004 and PIPF-006 for mean per cent predicted FVC values (69.8% compared with 73.1–76.4%) and DLCO (38.6% compared with 46.1–47.8%). In addition, oxygen use was higher for patients in the named patient programme (36%) than in PIPF-004 (14–17%) and PIPF-006 (28%). The manufacturer stated that these results indicated that the population in
PIPF-004 and PIPF-006 had slightly milder disease than the population in the named patient programme. It noted that the demographics, baseline concomitant disorders, and medication were largely comparable between the population in the clinical trials and the named patient programme. The manufacturer also presented results for the subgroup of patients with baseline FVC 80% predicted or less. These results are confidential.

**Subgroup analyses**

3.18 The manufacturer analysed the primary outcome results for per cent predicted FVC according to subgroups defined by baseline patient characteristics: gender, age, race, geographic region, time since diagnosis (less than 1 year or 1 year or more), baseline severity of disease (predicted FVC less than 70%, 70–80% or 80% or greater), baseline oxygen use and baseline oxygen use during the 6-minute walk test. 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. In the pooled analysis, the manufacturer noted that there was no evidence of interaction between treatment and gender, age, race, geographic region and baseline severity of disease.

3.19 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 the subgroups of baseline severity of disease according to per cent predicted FVC. The manufacturer's submission did not provide an interpretation of the data presented. However, the 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 80% predicted or higher. There was evidence of quantitative interaction in the subgroups according to the time from diagnosis to randomisation (p=0.021); the treatment effect was in favour of pirfenidone in both subgroups, but was larger in those diagnosed 1 year or more before randomisation.

3.20 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 80% predicted or less. In its
response to consultation, the manufacturer noted that this subgroup represented 69% of the total randomised population in the 2 studies. 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 80% predicted or less, the decrease observed in per cent predicted FVC was statistically significantly lower at 72 weeks with pirfenidone compared with placebo in the pooled analyses (−8.4% compared with −12.7%, p=0.0052). However, the manufacturer stated that there was no statistically significant difference between the pirfenidone and placebo group in patients with baseline per cent predicted FVC greater than 80% (−8.6% compared with −7.4%, p=0.2979). Results for other time points are confidential. In response to consultation, the manufacturer presented additional data for the change in FVC from baseline to 72 weeks in patients with baseline FVC 80% predicted or less from each of the 2 studies and clarified that the individual patient data were analysed in the same way for the subgroup as for the full trial population.

3.21 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 80% predicted or less. The manufacturer indicated that in this subgroup there was a statistically significant reduction for patients receiving pirfenidone compared with placebo in the risk of disease progression or death (28.2% compared with 35.8%, hazard ratio 0.68 [95% CI 0.49 to 0.94], p=0.0196), all-cause mortality (7.8% compared with 13.3%, hazard ratio 0.56 [95% CI 0.31 to 0.99], p=0.0424) and mortality related to idiopathic pulmonary fibrosis (4.9% compared with 12.0%, hazard ratio 0.39 [95% CI 0.20 to 0.77], p=0.0048).

Indirect comparison

3.22 The manufacturer performed an indirect comparison of pirfenidone with triple therapy (N-acetylcysteine, azathioprine and a corticosteroid) using the interim results for the placebo and triple-therapy arms of the PANTHER study (which compared triple therapy with N-acetylcysteine alone and with placebo in patients with idiopathic pulmonary fibrosis). 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.
fibrosis in the pooled PIPF-004 and PIPF-006 studies. 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 80% predicted or less.

Meta-analyses

3.23 The manufacturer stated 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 a corticosteroid 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).

3.24 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.

3.25 In a meta-analysis of FVC using a fixed-effects model for PIPF-004 and PIPF-006, the manufacturer reported a statistically significant standardised mean difference in per cent predicted FVC of 0.20 between the pirfenidone and placebo groups (95% CI 0.05 to 0.35, p=0.01). The manufacturer identified substantial heterogeneity ($I^2=71\%$) but was unable to determine the reason for the heterogeneity between the 2 near-identical trials. The results of a meta-analysis of FVC and VC that included PIPF-004, PIPF-006 and SP3 studies are confidential. The manufacturer did not identify any heterogeneity for other outcomes including change in FVC over time, progression-free survival, worsening of idiopathic pulmonary fibrosis, quality of life (St George’s Respiratory Questionnaire and World Health Organization score for health-
related quality of life), change in dyspnoea, DLco and worst SpO2. The results of a meta-analysis of all-cause mortality that included PIPF-004, PIPF-006, SP3 and SP2 are confidential.

3.26 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 manufacturer considered that a fixed-effects model was the most appropriate for these subgroup analyses because the trials had identical selection criteria. The first subgroup was patients with baseline FVC 80% predicted or less. A fixed-effects model was used 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. For the comparison of pirfenidone and placebo, 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. A statistically significant 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 pirfenidone were also reported. The manufacturer noted substantial heterogeneity (I^2 greater than 60%) for all of these outcomes except 6-minute walk test distance.

3.27 The manufacturer identified a second post-hoc subgroup of patients with baseline FVC 80% predicted or less who had borderline obstructive disease (defined as an FEV1/FVC ratio of less than 0.8, where FEV1 is forced expiration volume in 1 second). The manufacturer explained that there was a higher proportion of patients with borderline obstructive disease in the placebo arm of PIPF-006 than in the pirfenidone arm, and indicated that this could account for the difference in the FVC results between PIPF-004 and PIPF-006. The manufacturer did not present meta-analysis results for the subgroup of patients with baseline FVC 80% predicted or less excluding patients with borderline obstructive disease, which was the subgroup incorporated into its economic model, but noted 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

3.28 The main safety data in the manufacturer’s submission related to a combined patient population from PIPF-004 and PIPF-006, which included 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%).

3.29 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 the combined patient population from PIPF-004 and PIPF-006. The results of a meta-analysis of adverse effects that combined data from PIPF-004, PIPF-006 and SP3 are confidential.

3.30 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 or rash was lower in the PIPF-012 extension study than in the earlier PIPF-004 and PIPF-006 studies (19.7% compared with 44.4%), and that 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%).

3.31 In response to consultation, the manufacturer cited an abstract presented at the British Thoracic Society Winter Meeting 2012 to demonstrate that the adverse effects of treatment with pirfenidone did not significantly affect the quality of life of patients in clinical practice, which included safety data from the named patient programme. In an analysis of 68 patients, data were available for 53 patients at 3 months. Of these, 42 (79.2%) continued to receive pirfenidone and 11 (20.8%) had stopped therapy. Between 3 and 6 months, 93.1% (27/29) continued pirfenidone and 2 further patients (6.9%) stopped treatment. Out of a total of 68 patients, 30 (44.1%) experienced an adverse drug reaction resulting in a change of dose or discontinuation. After dose reduction, some of these patients were able to continue therapy (12/22 [54.5%] patients with data available). The manufacturer also highlighted the findings of a single-centre observational study that investigated the impact of the adverse effects of
Pirfenidone on quality of life in patients participating in the named patient programme (n=26). There was a downward trend in all domains of the Self-Report Chronic Respiratory Disease Questionnaire, for which high scores indicate a lower quality of life, but no relationship was found between quality-of-life scores and adverse effects.

Cost effectiveness

3.32 The manufacturer was unable to identify any published cost-effectiveness studies that were relevant to the decision problem. The manufacturer submitted a de novo microsimulation 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 was based on the total pooled patient population for PIPF-004 and PIPF-006 and a subgroup analysis investigating the patients with baseline FVC 80% predicted or less. The analysis was conducted from an NHS and personal and social services perspective. A lifetime time horizon (60 years) was used and a 3.5% discount rate was adopted for health benefits and costs.

3.33 The manufacturer subsequently 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.

3.34 The manufacturer advised that it had made further changes in its second model:

- Discontinuation rates were 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).

- A miscalculation in the average number of pirfenidone capsules was corrected.

- End-of-life costs for deaths unrelated to idiopathic pulmonary fibrosis were excluded.

- An additional subgroup was modelled: patients with baseline FVC 80% predicted or less excluding patients with borderline obstructive disease (defined as an FEV₁/FVC ratio of less than 0.8).
3.35 The manufacturer's microsimulation model sampled 647 of the 692 patients in PIPF-004 and PIPF-006 who had all of the desired baseline characteristics (gender, age, FVC and 6-minute walk test distance) recorded. It 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 in patients with idiopathic pulmonary fibrosis, but with a similar study design to PIPF-004 and PIPF-006), which it stated would enable 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 1 of 6 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).

3.36 In the first and second models, probability of death related to idiopathic pulmonary fibrosis in a 24-week period was based on a logistic regression analysis that used FVC and 6-minute walk test distance as independent variables. The manufacturer found that using the logistic regression underpredicted the proportion of deaths at 72 weeks with best supportive care compared with PIPF-004 and PIPF-006 (4.7% compared with 7.2%). Conversely, the manufacturer found that using the logistic regression overpredicted the proportion of deaths at 72 weeks with pirfenidone compared with the clinical trials (4.4% compared with 3.9%). To correct for this, the probability of death related to idiopathic pulmonary fibrosis for the comparison of pirfenidone and best supportive care was calibrated to the 72-week mortality from the PIPF-004 and PIPF-006 trials using an adjustment factor for each treatment.
This was the ratio of the proportion of death in the 2 arms of the trials to the predicted proportion from the regression. For the comparison of pirfenidone and triple therapy, the probability of death was calibrated to the mortality related to idiopathic pulmonary fibrosis at 72 weeks in PIPF-004 and PIPF-006, and to the all-cause mortality at 60 weeks in the PANTHER study. The manufacturer found that overall survival was predicted well by this method and suggested that the predicted median survival for the best supportive care group was clinically realistic (the predicted value is confidential). The probability of death unrelated to idiopathic pulmonary fibrosis was based on all-cause mortality rates for the UK population. Probability of hospitalisation in a 24-week period was also based on a logistic regression analysis that used FVC and 6-minute walk test distance as independent variables.

3.37 In response to consultation, the manufacturer submitted a third model, which added age and gender as independent covariates to the regression equation used to calculate idiopathic pulmonary fibrosis-related mortality, risk of hospitalisation and the St George's Respiratory Questionnaire scores. It reported that this did not improve the goodness of fit of the regressions for idiopathic pulmonary fibrosis-related mortality and hospitalisation.

3.38 The manufacturer explained that because the quality-of-life data from the pirfenidone clinical trials were only available up to 72 weeks, the St George's Respiratory Questionnaire scores used in its economic model were predicted by linear regression using FVC and the 6-minute walking test distance as independent variables. 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 using an algorithm that was estimated using data for patients with chronic obstructive pulmonary disease. 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.

3.39 In response to consultation, the manufacturer attempted to address uncertainty in the estimation of quality of life. The manufacturer updated the regressions by mapping the predicted St George's Respiratory Questionnaire score onto the EQ-5D using data from patients with idiopathic pulmonary fibrosis. When the manufacturer added age and gender as independent covariates to the
regressions in its third model, it found that this improved the goodness of fit for the predicted St George's Respiratory Questionnaire score. The methods and results of the mapping exercise are confidential.

3.40 The treatment-associated costs for each cycle for the pirfenidone group comprised the cost of the technology plus oxygen and monitoring costs. Only oxygen and monitoring costs were applied to the best supportive care group. In response to consultation, a second patient access scheme was applied in the manufacturer's third economic model, with a simple confidential discount to the list price of pirfenidone. The second patient access scheme superseded the first one, which had been applied to the results of the second model in the same way. The manufacturer assumed that there are no costs associated with implementing and operating the scheme. The annual total costs for triple therapy were based on prices in the latest 'Monthly index of medical specialities' (MIMS; prednisolone and azathioprine) or expert opinion (N-acetylcysteine). 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 NHS Regional Drugs and Therapeutic Centre.

3.41 Costs for each of the 6 health states 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). For best supportive care, the health state costs ranged from £800 (alive, not hospitalised) to £24,456 (death related to idiopathic pulmonary fibrosis, hospitalised). Health state costs for pirfenidone are confidential. 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 hospital stay 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.

3.42 Costs for managing treatment-associated adverse effects of pirfenidone were not included because the manufacturer stated that 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 how any costs of managing treatment-associated adverse effects of triple therapy would be captured by the model.

3.43 The manufacturer found that, after calibration, the model exactly replicated the PIPF-004 and PIPF-006 clinical trial data for 72-week mortality related to idiopathic pulmonary fibrosis for best supportive care (7.2%) and pirfenidone (3.9%) and the associated hazard ratio (0.53). The manufacturer stated that it anticipated that the hazard ratio would be 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 according to change in St George's Respiratory Questionnaire score with best supportive care and pirfenidone, but felt that the model results would not be greatly affected because the relative difference and absolute value were fairly similar. The manufacturer did not discuss how well the model predicted quality of life with triple therapy.

3.44 In response to consultation, the manufacturer presented extrapolated overall survival curves for patients with baseline FVC 80% predicted or less generated using the third model, which were overlaid with Kaplan–Meier plots for patients taking placebo in PIPF-004 and PIPF-006 and patients taking pirfenidone in PIPF-004 and PIPF-006 who then continued into PIPF-012. The manufacturer observed that the extrapolated pirfenidone survival curve closely followed the Kaplan–Meier plot for pirfenidone up to 204 weeks, and that the extrapolated placebo curve predicted survival well when compared with the Kaplan–Meier plot up to week 72 (data after 72 weeks were considered unreliable because of attrition in the placebo arms). The manufacturer considered its predicted median survival estimate in the placebo arm to be conservative, because clinical specialists and the published literature suggested it is at the higher end of reported median survivals.
The manufacturer did not present cost-effectiveness estimates incorporating the first patient access scheme for the whole population with mild-to-moderate idiopathic pulmonary fibrosis, but instead presented base-case analyses in the subgroup of patients with baseline FVC 80% predicted or less. The incremental cost-effectiveness ratios (ICERs) for pirfenidone were £36,327 per QALY gained compared with best supportive care, £16,560 per QALY gained compared with triple therapy and £29,467 per QALY gained compared with the pooled comparator. Incremental costs and QALYs are confidential.

The manufacturer presented cost-effectiveness results incorporating the first patient access scheme for pirfenidone compared with best supportive care, triple therapy and a pooled comparator in the subgroup of patients with baseline FVC 80% predicted or less, excluding patients with borderline obstructive disease. The ICERs for pirfenidone were £34,471 per QALY gained compared with best supportive care, £16,839 per QALY gained compared with triple therapy and £28,466 per QALY gained compared with the pooled comparator. Incremental costs and QALYs are confidential.

The manufacturer conducted univariate sensitivity analyses using its second model for the subgroup with baseline FVC 80% predicted or less, incorporating the first patient access scheme. The manufacturer reported that the results were sensitive to the discount rates for costs and outcomes and the number of pirfenidone capsules taken each day (values are confidential). In its scenario analyses, the manufacturer removed the effect of the adjustment factors used to calculate mortality related to idiopathic pulmonary fibrosis for patients receiving pirfenidone or best supportive care and indicated that the ICERs were sensitive to this (values are confidential). The manufacturer did not conduct analyses in which the adjustment factors for pirfenidone and best supportive care were both removed at the same time. Additionally, in the comparison of pirfenidone with triple therapy, the manufacturer noted low sensitivity to the adjustment factors used to replicate mortality related to idiopathic pulmonary fibrosis (values are confidential).

In response to consultation, the manufacturer presented base-case analyses using its third model, which incorporated the second patient access scheme, in the subgroup of patients with baseline FVC 80% predicted or less. The deterministic and probabilistic ICERs for pirfenidone compared with best supportive care were £25,969 per QALY gained and £24,062 per QALY gained.
Incremental costs and QALYs are confidential. No cost-effectiveness estimates for the whole population with mild-to-moderate idiopathic pulmonary fibrosis were provided.

3.49 In response to consultation, the manufacturer repeated its probabilistic sensitivity analyses and conducted additional structural and scenario analyses for the subgroup with baseline FVC 80% predicted or less using its third model, which incorporated the second patient access scheme. The additional analyses included the regression coefficients for idiopathic pulmonary fibrosis-related mortality, hospitalisation and St George's Respiratory Questionnaire, the calibration factors and the St George's Respiratory Questionnaire mapping coefficients. The results of the manufacturer's probabilistic sensitivity analyses incorporating the second patient access scheme for the subgroup with baseline FVC 80% predicted or less are confidential and so are not reported here.

Evidence Review Group comments

Clinical effectiveness

3.50 The ERG considered 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 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 on decline in FVC 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.

3.51 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 the 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 or VC values of 73–81% across the 4 randomised controlled trials) was likely to be lower in the trials than in UK clinical practice. In addition, the ERG indicated that there were limitations with the accuracy of FVC in measuring disease severity.

3.52 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 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 and thus could have contributed to the observed outcomes. The ERG also described the following limitations associated with the indirect comparison of pirfenidone and triple therapy carried out 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 80% predicted or less on the whole group data from the PANTHER study compared with the subgroup data from the pirfenidone studies.

3.53 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**

3.54 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 stated that there appeared to be no clear reason why there were statistically significant
differences between pirfenidone 2403 mg/day and placebo groups for some outcomes in PIPF-004 but not in PIPF-006.

3.55 The ERG found 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) showing that a decline in per cent predicted FVC of 5–10% had prognostic significance for individual patients and that the minimally important clinical difference for a cohort with idiopathic pulmonary fibrosis was calculated as 2–6% of predicted normal values.

3.56 The ERG 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.

Subgroup analyses

3.57 The ERG highlighted uncertainties in the manufacturer's submission regarding the subgroup analysis of change in FVC according to baseline patient characteristics, and advised caution in interpreting the results. It observed that although the results generally favoured pirfenidone 2403 mg/day, the confidence intervals were wide and often crossed the line of no effect.

3.58 The ERG reviewed the analysis of the subgroup with baseline FVC 80% predicted or less excluding patients with borderline obstructive lung disease, and considered that the manufacturer presented a reasoned case for the possibility that a greater proportion of patients in this subgroup were assigned to placebo in PIPF-006 and this contributed to the difference in efficacy between the PIPF-004 and PIPF-006 studies. The ERG queried the validity of the threshold of airflow obstruction chosen by the manufacturer for the definition of borderline obstructive lung disease, noting that Management of chronic obstructive pulmonary disease in adults in primary and secondary care

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(NICE clinical guideline 101) stipulated a threshold of \( \text{FEV}_1/\text{FVC} \) less than 0.7 to define airflow obstruction. 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.

Cost effectiveness

3.59 The ERG noted that the manufacturer's cost-effectiveness analysis met the requirements of the NICE reference case and was generally appropriate. The ERG found the changes made in the manufacturer's second model to be reasonable, including the updated discontinuation rates and increased patient numbers in the sampled population, as was the assumption that the mortality did not change, and noted a small impact on the ICER. The ERG verified that the results obtained with the manufacturer's second model were consistent with the original version but was unable to check data for the discontinuation rates or capsules per day.

3.60 The ERG noted that the hypothetical mild-to-moderate population simulated 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.

3.61 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 economic model.

3.62 The ERG cited concerns about the reliability of the comparison of pirfenidone and triple therapy that was presented in the manufacturer's second economic model. The concerns included uncertainty in the discontinuation rates taken from the PANTHER study and weaknesses in the data used for the indirect comparison. In addition, the ERG had further concerns about how the data had been incorporated into the manufacturer's second economic model after checking the results from the analyses for triple therapy. The ERG noted that about 11% of patients in the triple-therapy arm in the PANTHER study died within 6 months but that the manufacturer's model predicted a far greater
proportion of deaths (this value is confidential). Furthermore, the ERG noted that the analyses for the subgroup with FVC 80% predicted or less and the subgroup with FVC 80% predicted or less excluding patients with borderline obstructive lung disease assumed even higher mortality rates for the triple-therapy group at 6 months (these values are confidential).

3.63 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 second 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.

3.64 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 1 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 analyses using the pooled comparator.

3.65 The ERG noted that not all model parameters had been included in the univariate or probabilistic sensitivity analyses in the manufacturer’s first and second models, including key parameters associated with overall survival, hospitalisation and quality of life. It advised that consequently the full uncertainty around these model results had not been shown.
3.66 Following the manufacturer’s response to consultation, the ERG found that the deterministic sensitivity analyses using the third model contained all the most influential parameters and structural assumptions. However, it noted that the submission did not report how uncertainty around the hazard ratios was applied. Furthermore, the ranges used for the deterministic and probabilistic sensitivity analyses were not listed. The ERG concluded that it was not possible to comment on either the reliability or the validity of the results of the deterministic and probabilistic sensitivity analyses.

3.67 The ERG noted uncertainty around the cost-effectiveness analysis of the subgroup of patients with FVC 80% predicted or less, and the subgroup of patients with FVC 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.

3.68 The ERG noted that although the manufacturer stated its patient access scheme is available to all patients with mild-to-moderate idiopathic pulmonary fibrosis, it did not provide analyses including the scheme for the whole population, but only for the 2 subgroups (patients with FVC 80% predicted or less, and patients with FVC 80% predicted or less excluding patients with borderline obstructive disease). The ERG checked the subgroup results incorporating the first patient access scheme discount and considered them to be consistent with those for the subgroup analyses that did not incorporate the patient access scheme. However, the ERG concluded that these results should be interpreted cautiously because of the lack of a robust evidence base.

3.69 Following the manufacturer’s response to consultation, the ERG checked the results for the third model and analysed the individual impact of the updated St George's Respiratory Questionnaire mapping equation. The results of this analysis are confidential. The ERG was unable to check the individual effects of age and gender as independent covariates because the change was within the visual basic coding and could not be replicated in the time available, but advised that it did not anticipate that these would have a significant effect on the ICER.
ERG exploratory analyses

3.70 The ERG conducted several additional exploratory 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.

3.71 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 considerably and over a wider range than that reported by the manufacturer in its scenario analyses (these ICERs are confidential). When the model was run using the upper confidence limits of all coefficients for the relevant regression equations, the ERG found that the ICERs decreased (these ICERs are confidential). No analysis was conducted using the lower confidence limits of all the coefficients for the regression equations.

3.72 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). These values for the idiopathic pulmonary fibrosis-related mortality hazard ratio were obtained using different estimates for the adjustment factor for pirfenidone treatment while keeping the base-case adjustment factor for best supportive care constant. At the lower limit of the 95% confidence interval, the ERG noted that the ICER for pirfenidone compared with best supportive care decreased (values are confidential). When the upper limit was used, the ERG found that the ICER increased (this ICER is confidential).

3.73 The ERG found that the ICER was highly sensitive to changes in patients' quality of life. Patients' quality of life was over- and underestimated 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 and assuming the same length of hospital stay in the pirfenidone and best supportive care arms had little impact on the ICER (these ICERs are confidential).
3.74 The ERG applied the first patient access scheme to the population of patients with mild-to-moderate idiopathic pulmonary fibrosis and found that this gave an ICER greater than £36,327 per QALY gained (the value is confidential; it can only be stated that it is greater than the manufacturer's ICER incorporating the first patient access scheme for the comparison of pirfenidone with best supportive care in the subgroup of patients with FVC 80% predicted or less). The ERG gave its opinion on the probability of pirfenidone being cost effective at a range of £20,000 to £30,000 per QALY gained (this value is confidential).

3.75 Following the manufacturer's response to consultation, the ERG applied the second patient access scheme to the population of patients with mild-to-moderate idiopathic pulmonary fibrosis using the manufacturer's third model and found that it gave a deterministic ICER greater than £25,969 per QALY gained (the value is confidential; it can only be stated that it is greater than the manufacturer's ICER incorporating the second patient access scheme for the comparison of pirfenidone with best supportive care in the subgroup of patients with FVC 80% predicted or less).

3.76 Full details of all the evidence are in the manufacturer's submission and the ERG report.
4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the 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 specialists. It also took into account the effective use of NHS resources.

4.2 The Committee discussed the treatment pathway for idiopathic pulmonary fibrosis. It heard from clinical specialists that there may be variation in care depending on whether this is in a specialised centre or not and because of a lack of recognised care pathways in some parts of the country. It also heard from clinical specialists how an accurate diagnosis is pivotal when starting treatment for idiopathic pulmonary fibrosis and that current initial treatment options included N-acetylcysteine, observation and best supportive care and participating in a clinical trial. The clinical specialists advised that idiopathic pulmonary fibrosis is a highly heterogeneous condition and that it is difficult to predict which patients might respond well to treatment or might be more likely to experience adverse effects. They added that no drug or treatment has yet shown a survival benefit in treating idiopathic pulmonary fibrosis. The Committee heard from the clinical specialists that it would be preferable to use drugs that modify the natural history of the disease early in the treatment pathway, before irreversible damage occurs (for example, honeycomb lung and fibrosis). The Committee acknowledged the challenges of treating idiopathic pulmonary fibrosis and recognised the need for new effective treatment options to inhibit disease progression.

4.3 The Committee heard from patient experts about the impact of idiopathic pulmonary fibrosis and its treatment on daily life. It heard that the symptoms of the disease can have a debilitating effect and that dependency on oxygen treatment can limit activities of daily living. It noted the benefit of non-pharmacological interventions such as pulmonary rehabilitation. It heard that patients needed hope and would place high value on any new treatment that could prevent symptoms from worsening, decrease dependency on oxygen, increase survival and reduce hospitalisation. The Committee acknowledged the demands that living with idiopathic pulmonary fibrosis can place on patients and accepted there was a need to lessen these.
4.4 The Committee examined the clinical trial evidence for pirfenidone that had been submitted by the manufacturer. The Committee noted that the FDA had highlighted that, according to the study protocols, the secondary outcome variables should only be analysed using pooled data from PIPF-004 and PIPF-006 if the primary efficacy end points from each study were achieved. The manufacturer confirmed that this was the case but nevertheless considered that analysing pooled data from these 2 trials was justified. The Committee observed that the European Medicines Agency had accepted the pooled analyses. The Committee noted the near-identical design of these 2 studies and agreed that analyses of the pooled data were reasonable. Overall, the Committee concluded that the trials provided evidence that was adequate for currently assessing the clinical effectiveness of pirfenidone in idiopathic pulmonary fibrosis.

4.5 The Committee discussed the definition of ‘mild-to-moderate’ idiopathic pulmonary fibrosis (which is the indication covered by pirfenidone's UK marketing authorisation). It was uncertain how the population covered by the marketing authorisation related to the patient population in the clinical trials. It heard from the clinical specialists that although there are no recognised criteria for defining these disease stages, it is widely accepted that severe idiopathic pulmonary fibrosis is defined as FVC less than 50% predicted and \( \text{DL}_{\text{CO}} \) less than 35% predicted and that these patients would have been excluded from the clinical trials. Although the Committee had some reservations about the lack of an upper limit of per cent predicted FVC in the clinical trials, it concluded that the clinical trial design allowed an acceptable estimate of pirfenidone's effectiveness in mild-to-moderate pulmonary fibrosis with the currently available data. The Committee was aware of the ASCEND study, which will be the largest randomised study of pirfenidone compared with placebo in mild-to-moderate idiopathic pulmonary fibrosis, and that the results are expected to be available in 2014.

4.6 The Committee reviewed the generalisability of the patient population in PIPF-004 and PIPF-006 to the UK patient population. The Committee had concerns that the full trial population had milder idiopathic pulmonary fibrosis and fewer comorbidities than typically seen in UK clinical practice. It heard from the clinical specialists that it is relatively rare for patients with confirmed idiopathic pulmonary fibrosis to have FVC greater than 80% predicted. The Committee was aware of the results of the named patient programme and of the manufacturer's conclusion that these supported the use of pirfenidone in
patients with FVC 80% predicted or less. The Committee heard from the clinical specialists that the higher discontinuation rates and greater toxicity observed in the named patient programme were likely to be related to the limited experience clinicians had with using pirfenidone, and these would lessen as greater experience was gained. The Committee concluded that there were some differences in disease severity and comorbidities between the full patient population in the clinical trials and those seen in UK clinical practice. Although the Committee considered that there was an issue of generalisability from the full clinical trial populations to people with idiopathic pulmonary fibrosis in clinical practice in England and Wales, it was prepared to consider the clinical trials appropriate for estimating the effectiveness of pirfenidone in the absence of any alternative evidence.

4.7 The Committee discussed triple therapy with N-acetylcysteine, azathioprine and prednisolone as a comparator for pirfenidone. It noted the recent publication of the interim results of the PANTHER study, which showed increased mortality and hospitalisation with triple therapy compared with placebo. The clinical specialists explained that the use of triple therapy within the NHS is declining after the publication of the PANTHER study results and the guidance issued by professional organisations such as the British Thoracic Society, which has recommended that patients should no longer start on triple therapy and those already taking this combination should discontinue if there is any deterioration. The Committee concluded that, although specified in the NICE scope, triple therapy was no longer routine or best practice in the NHS for patients starting treatment for idiopathic pulmonary fibrosis and could no longer be considered a comparator for pirfenidone.

4.8 The Committee discussed whether treatment with placebo in the clinical trials could be considered equivalent to best supportive care in UK clinical practice. It had concerns over the lack of standardisation of best supportive care at the different centres participating in the clinical trials because randomisation was stratified by region and not by centre. However, it recognised that patients taking placebo in clinical trials tend to receive high-quality care at centres of excellence, and heard from the clinical specialists that the assumption seemed reasonable given that routine best supportive care in the UK would not include immunosuppressants such as azathioprine. The Committee concluded that it was acceptable to consider the treatment given in the placebo arms of the clinical trials to be equivalent to best supportive care in UK clinical practice.
4.9 The Committee discussed the clinical effectiveness of pirfenidone in treating mild-to-moderate idiopathic pulmonary fibrosis. It noted that in 1 trial (PIPF-004), pirfenidone demonstrated a statistically significant difference in mean change in per cent predicted FVC at 72 weeks (absolute difference 4.4% between the pirfenidone and placebo groups), but in another similar trial (PIPF-006) there was no statistically significant difference between groups (absolute difference 0.6% in favour of pirfenidone). However, it also noted the statistically significant difference in mean change in per cent predicted FVC in a pooled analysis of the 2 studies (absolute difference 2.5% in favour of pirfenidone). The Committee further observed that the absolute difference in median FVC was the same in both trials (1.1%) and considered this was likely to be because of imputing a 0% change for FVC at 72 weeks for patients who had died, which it interpreted to signify that the means are sensitive to extreme values (which affect the mean value and not the median). It noted that the evidence suggested pirfenidone had a modest effect on reducing the decline in FVC but was unsure if this was clinically meaningful. It noted that the European Medicines Agency had concluded that pirfenidone produced a measurable improvement in the absolute change in per cent predicted FVC, as shown in the pooled analysis of PIPF-004 and PIPF-006, and that this was modest but meaningful. The Committee agreed that the 2.5% absolute difference in FVC decline at 72 weeks in the mild-to-moderate population could be considered clinically significant, but that a sustained benefit was uncertain given the short duration of PIPF-004 and PIPF-006 and the differences between the results of the 2 studies. The Committee noted that there were no FVC data available for patients who had received pirfenidone in PIPF-004 and PIPF-006 and continued with pirfenidone in PIPF-012 (although 60-week FVC data from PIPF-012 were available for patients who had switched from placebo to pirfenidone). The Committee concluded that pirfenidone seemed to have a modest but measurable effect on slowing the decline in lung function, but that there was uncertainty in whether this benefit persisted over time because of the lack of data on pirfenidone’s effect on lung function beyond 72 weeks of treatment.

4.10 The Committee considered the differences in outcomes between PIPF-004 and PIPF-006. It noted that PIPF-004, but not PIPF-006, met its primary outcome of a statistically significant difference in change in FVC at 72 weeks between the pirfenidone and placebo groups and that statistically significant differences between groups were detected for only 1 secondary outcome, which differed in each study (progression-free survival in PIPF-004 and 6-minute walk test
distance in PIPF-006). It noted that if clinical trials have met their primary end points, the differences between treatment groups are generally supported by the results of the secondary end points. It found that in the pooled analysis, however, there was no difference between treatment groups in many of the secondary outcomes including worst SpO\textsubscript{2} during the 6-minute walk test, dyspnoea, quality of life, time to worsening of idiopathic pulmonary fibrosis, exacerbation rates and overall mortality. It accepted that there was no clear explanation for the different results between PIPF-004 and PIPF-006, but was aware that the placebo group in PIPF-006 experienced less decline in FVC than expected, which could potentially be explained by the higher proportion of patients with borderline obstructive disease (FEV\textsubscript{1}/FVC less than 0.8) in this study. The Committee concluded that although it had concerns about the differences in the results of the 2 studies (particularly in relation to the outcomes considered important to people with idiopathic pulmonary fibrosis), the pooled analysis of the primary end point of PIPF-004 and PIPF-006 provided acceptable evidence of pirfenidone's overall modest treatment effect over a short duration.

4.11 The Committee reviewed the acceptability of the adverse effects associated with pirfenidone. The manufacturer stated that around 80–90% of adverse effects were grade 1 and 2 and the Committee heard from the clinical specialists that the adverse effects were generally transient and usually resolved if the dose of pirfenidone was reduced or temporarily discontinued. The Committee accepted that the data from the PIPF-012 extension study showed that longer-term adverse effects were similar to those seen in the randomised trials, but noted that the results from the named patient programme suggested that dose reductions and discontinuations may be higher than in the randomised trials. It concluded that pirfenidone's adverse-effect profile was acceptable in a severe disease such as idiopathic pulmonary fibrosis, but that it was also significant given the potential long-term administration of pirfenidone.

4.12 The Committee discussed the reliability of the idiopathic pulmonary fibrosis-related mortality data. It had reservations about the lack of statistical power to detect a difference in mortality, and the short duration of the randomised controlled trials. The Committee also recognised the concerns in the European public assessment report, which indicated that data from PIPF-004 and PIPF-006 showing a reduction in mortality were based on observational data and derived from small numbers, and that substantiating the claim would
require a proper outcome study over several years. It noted the consultation responses that stated that it is unlikely clinical trials for idiopathic pulmonary fibrosis treatments will ever be powered to detect a difference in mortality. The Committee was also concerned that the 72-week duration of PIPF-004 and PIPF-006 did not provide sufficient information about the persistence of treatment effect. It noted that in response to consultation the manufacturer had provided additional mortality data from the PIPF-012 extension study for patients who had received treatment with pirfenidone for up to 4 years. The Committee concluded that although there was uncertainty about a possible survival benefit based on the data from PIPF-004 and PIPF-006 because of the small number of events and short follow-up, this was the only evidence available for decision-making.

4.13 The Committee discussed the hospitalisation data that were obtained in PIPF-004 and PIPF-006. It sought to verify the difference in length of hospital stay between patients receiving placebo and those receiving pirfenidone. The Committee noted that data showing mean length of stay had been presented and was uncertain if the median data would be similar, or if a small number of patients who had a prolonged period of hospitalisation had skewed the mean data. However, the median data were not included in the manufacturer's submission so the Committee was not able to confirm whether there was any difference between the figures for the mean and median lengths of stay for pirfenidone and placebo in the pooled trial analyses. The Committee concluded that the mean data for length of hospital stay were acceptable for evaluation because these were the only data available.

4.14 The Committee discussed the clinical validity of the 2 subgroups of patients presented by the manufacturer (FVC 80% predicted or less, including or excluding patients with borderline obstructive disease). The clinical specialists advised that in clinical practice they saw few patients who had idiopathic pulmonary fibrosis with FVC greater than 80% predicted and noted the clinical relevance of the subgroup of patients with FVC 80% predicted or less to clinical practice. The Committee heard that treatment decisions were made after taking multiple factors into account (such as symptoms and degree of deterioration) and would not be wholly based on lung function test results. It also heard from the clinical specialists that FVC 80% predicted or less was an arbitrary but acceptable threshold for initiating treatment for idiopathic pulmonary fibrosis and that this could be easily implemented in clinical practice. The Committee
observed that the stratification for FVC in the PIPF-004 and PIPF-006 trials had been into 3 groups: baseline FVC less than 70% predicted, baseline FVC 70% to less than 80% predicted, and baseline FVC 80% predicted or greater. The clinically relevant subgroup analysis of FVC 80% predicted or less was therefore very close to, but did not exactly match, the stratification criteria. The Committee concluded that the subgroup of patients with FVC 80% predicted or less was clinically relevant and acceptable for making treatment decisions in clinical practice.

4.15 The Committee then discussed the robustness of the clinical evidence for these 2 subgroups of patients. It was concerned that the analyses were post hoc and not statistically powered to detect a difference between treatments, and noted that the group with FVC 80% predicted or less was 69% of the whole PIPF-004 and PIPF-006 trial populations. However, the Committee acknowledged the practical difficulties in powering studies to detect mortality differences when conducting such trials, and also noted that the duration of the trials was longer than other trials evaluating idiopathic pulmonary fibrosis treatments. The Committee concluded that although the estimates of effectiveness derived from the subgroup analyses based on the FVC predicted value were not statistically robust it was reasonable to consider the results of these analyses because the subgroup with FVC 80% predicted or less more closely reflected the population with idiopathic pulmonary fibrosis in England and Wales than the full trial population.

4.16 The Committee discussed the manufacturer's general approach to developing its economic model. The Committee was uncertain why a microsimulation model using individual patient data had been chosen instead of a cohort model and had reservations over its complexity and lack of transparency. The manufacturer indicated that this approach took account of the heterogeneity of the disease and that using FVC and 6-minute walk test distance as covariates to predict mortality related to idiopathic pulmonary fibrosis was more powerful than using survival rates generated in the trials. It stated that this was because there were few deaths (less than 10%) in the first 72 weeks and patient numbers decreased markedly short afterwards in terms of known follow-up. The Committee accepted that using age, gender, FVC and 6-minute walk test distance as covariates to predict survival in a microsimulation model was an acceptable approach to modelling the natural history of idiopathic pulmonary fibrosis. The Committee concluded that the outlined structure of the model
adhered to the NICE reference case for economic analysis and was acceptable for assessing the cost effectiveness of pirfenidone.

4.17 The Committee then questioned the validity of how the manufacturer had implemented this approach in modelling mortality related to idiopathic pulmonary fibrosis. It noted that the manufacturer had supplemented the pooled PIPF-004 and PIPF-006 data set using data from a similar study, GIPF-007, because the mortality related to idiopathic pulmonary fibrosis was low in PIPF-004 and PIPF-006. The Committee expressed doubts over the methods used by the manufacturer in subsequently calibrating the model to ensure mortality matched that at 72 weeks in PIPF-004 and PIPF-006. It noted that before calibration the model had underestimated mortality related to idiopathic pulmonary fibrosis for patients receiving best supportive care, whereas it had overestimated mortality for patients receiving pirfenidone (compared with the small number of deaths related to idiopathic pulmonary fibrosis in the pooled analysis; see section 3.36). The Committee observed that the reduced uncertainty in how FVC and 6-minute walk test distance predict mortality that had been gained by adding data from GIPF-007 was negated by fixing an additional treatment effect using adjustment factors calibrated to mortality data at 72 weeks, and noted that the manufacturer could similarly have adjusted the original parametric equations derived from PIPF-004, PIPF-006 and PIPF-012. It was also concerned that the manufacturer assumed that this treatment effect then persisted until death, although limited evidence for efficacy beyond 72 weeks had been presented in its submission. The Committee also heard that the clinical specialists felt that the life years gained for the different populations were generally higher than would be expected in clinical practice. The Committee further noted that the uncertainty of the mortality estimates would increase because of the errors accumulating at each stage generating the final estimate. The Committee was concerned that although the manufacturer had increased the discontinuation rates of pirfenidone from 72 weeks up to 192 weeks in the model based on the PIPF-012 extension study (which only included patients with known high adherence), the hazard ratios for survival based on data up to 72 weeks had been maintained for both the mild-to-moderate population and the subgroup with baseline FVC 80% predicted or less. The Committee concluded that there was considerable uncertainty in the survival rates generated by the model and was cautious in its interpretation of cost-effectiveness estimates produced using these data.
The Committee discussed the costs used in the economic model. It noted that the treatment cost for pirfenidone was based on capsules taken and not packs used and that this could lead to underestimation of the true treatment cost. The Committee had doubts about the difference in duration of hospital stay between treatment groups, expressing concern about a small number of patients with very significant durations of stay potentially biasing the mean. However, it noted that the ERG's analysis showed that assuming the same mean length of stay in hospital in both treatment arms did not substantially affect the ICER. The Committee concluded that there was some uncertainty in the treatment cost and health state costs, but did not anticipate that this would have a major effect on the cost-effectiveness estimates.

The Committee discussed how quality of life had been incorporated into the model. It queried why the clinical trial data had not been directly incorporated but instead the St George's Respiratory Questionnaire scores had been estimated using FVC and 6-minute walk test distance. It noted that uncertainty had been added in estimating health effects selected in the model, when predicting the St George's Respiratory Questionnaire score using age, gender, FVC and 6-minute walk test distance, and then when mapping the St George's Respiratory Questionnaire to the EQ-5D. The Committee further noted the effect on the results of the manufacturer's third model of mapping the St George's Respiratory Questionnaire to EQ-5D using an algorithm based on patients with idiopathic pulmonary fibrosis instead of chronic obstructive pulmonary disease. The Committee observed that the ERG's scenario analyses using the original model that varied the patients' quality of life demonstrated this uncertainty, which was reflected in the sensitivity of the ICERs. The Committee heard from the ERG that the changes made to estimating health effects in the manufacturer's third model had reduced the uncertainty because the mapping algorithm was developed on a more appropriate patient population. The Committee noted that no decrement to quality of life had been applied in the model to account for adverse effects and the findings of the analyses of the named patient programme presented by the manufacturer in response to consultation. The Committee concluded that there was some uncertainty in the estimation of utilities using the manufacturer's model, but that the estimates were adequate for decision-making.

The Committee was aware that in the model pirfenidone was continued until death unless stopped by patient or clinician choice. The Committee concluded
on the basis of clinical advice that it was likely that in clinical practice patients would take pirfenidone for as long as it was considered to be of continued benefit and it was good clinical practice to discontinue treatment if it becomes apparent that the drug is not making a significant impact on the disease. The clinical specialists also informed the Committee of the consensus that a decline in FVC of 10% or more from a baseline pre-treatment value represents progressive disease, and so indicated that the discontinuation rates of pirfenidone were likely to be higher than those derived from the PIPF-012 study. Consequently the Committee concluded that treatment with pirfenidone would be discontinued in clinical practice if there was evidence of disease progression, defined as a decline in per cent predicted FVC of 10% or more within any 12-month period.

4.21 The Committee discussed the manufacturer's probabilistic sensitivity analyses that explored the uncertainty associated with its third model. It noted the additional analyses supplied by the manufacturer in response to consultation to quantify the uncertainty associated with the estimated treatment effects (survival, hospitalisation and health-related quality of life). It observed that the uncertainty associated with the adjustment factors for idiopathic pulmonary fibrosis-related mortality had not been determined, although the uncertainty associated with the treatment adjustment factors that influence the treatment effect had been explored. It noted that the ERG found that the deterministic sensitivity analyses contained all the most influential parameters and structural assumptions, but that it was not possible for the ERG to comment on the reliability or validity of the results of the deterministic and probabilistic sensitivity analyses because the ranges used for these analyses had not been listed by the manufacturer. The Committee concluded that there was some uncertainty associated with the estimates of treatment effect of pirfenidone and mortality related to idiopathic pulmonary fibrosis and thus with the life years gained and QALYs generated using the manufacturer's model, but that the level of uncertainty was acceptable for decision-making.

4.22 The Committee reviewed how triple therapy had been compared with pirfenidone in the manufacturer's economic model. It noted that the ERG regarded the analysis as flawed. It heard from the clinical specialists that the mortality estimates generated by the model were not plausible for the mild-to-moderate population or for the subgroup with FVC 80% predicted or less. It was also aware that the hazard ratio that was incorporated into the model for the
indirect comparison of triple therapy and pirfenidone was very uncertain. The Committee concluded that the comparison of pirfenidone with triple therapy was unrealistic and uncertain, and so should be disregarded.

4.23 The Committee discussed the use of a pooled comparator in the manufacturer's economic model. It noted the ERG's advice that an incremental analysis offered information that was more useful for health technology assessment. It considered that the indirect comparison of triple therapy was uncertain and that the modelling was flawed (as described in the previous section). The Committee concluded that the comparison of pirfenidone with the pooled comparator was unrealistic, uncertain and inappropriate, and so should be disregarded.

4.24 The Committee deliberated over the most plausible ICERs presented by the manufacturer and the ERG. It was persuaded that the subgroup results from patients with FVC 80% predicted or less could be used to inform treatment decisions in UK clinical practice, and that this was the most appropriate population for evaluation. It considered that triple therapy was no longer routine or best practice in the NHS for patients starting treatment for idiopathic pulmonary fibrosis, and so best supportive care should be considered the sole comparator for pirfenidone. The Committee therefore agreed that the most plausible ICER was for the comparison of pirfenidone with best supportive care in people who had idiopathic pulmonary fibrosis with FVC 80% predicted or less, incorporating the second patient access scheme. It noted that the manufacturer's probabilistic ICER was £24,000 per QALY gained. It concluded that this offered an acceptable cost-effectiveness estimate on which to begin to explore its further considerations.

4.25 The Committee discussed whether pirfenidone fulfilled the criteria for consideration as a life-extending, end-of life treatment. The Committee heard from the clinical specialists that life expectancy for patients with mild-to-moderate idiopathic pulmonary fibrosis would typically exceed 2 years. Having established that pirfenidone did not meet the criterion for short life expectancy, the Committee decided it was not necessary to make a decision about the population or extension to life criteria. The Committee concluded that pirfenidone did not fulfil the criteria to be considered as a life-extending, end-of-life treatment.
The Committee discussed whether pirfenidone was an innovative treatment. It considered that pirfenidone had an innovative mechanism of action and observed that pirfenidone is the first drug that has been shown to have an impact on idiopathic pulmonary fibrosis in terms of improving outcomes without the long-term side-effects of immunosuppressants. The Committee heard that pirfenidone was considered to be a valuable new therapy for a disease of high unmet need. On the basis of currently available evidence, the Committee did not consider the use of pirfenidone to be a step change in the management of idiopathic pulmonary fibrosis, given its modest effect observed over a short duration. The Committee observed that there were no additional gains in health-related quality of life over those already included in the QALY calculations and again recalled that the adverse effects associated with pirfenidone had not been incorporated into the estimation of utilities in the economic model. The Committee concluded that there were no additional QALYs that had not been incorporated into the economic model and the cost-effectiveness estimates.

The Committee discussed whether using pirfenidone to treat idiopathic pulmonary fibrosis represented a cost-effective use of NHS resources. It agreed that the clinical-effectiveness evidence supported demonstrable (though modest) health benefits. Having considered all the submitted economic evidence, the Committee found that the structure of the economic model was appropriate and sufficiently robust, its inputs and assumptions were plausible, it reflected the decision problem specified in the scope and its structural uncertainties had been explored. Taking all of this into account, the Committee considered that the manufacturer's probabilistic ICER of £24,000 per QALY gained for the comparison of pirfenidone with best supportive care in people with idiopathic pulmonary fibrosis and FVC 80% predicted or less and incorporating the second patient access scheme was plausible. Because this ICER was within the range normally considered to represent a cost-effective use of NHS resources and was associated with an acceptable level of uncertainty, the Committee concluded that pirfenidone should be recommended for treating idiopathic pulmonary fibrosis in people with FVC between 50% and 80% predicted.

The Committee considered whether NICE’s duties under the equalities legislation required it to alter or to add to its recommendations. It noted that it was raised at consultation that idiopathic pulmonary fibrosis predominantly
affects older people. Because its recommendation applied equally to all people with idiopathic pulmonary fibrosis, regardless of age, the Committee concluded that its decision on the use of pirfenidone would not have a particular impact on older people and that there was no need to alter or add to its recommendations.

4.29 The Committee was aware that the ASCEND study is scheduled to report in 2014. It noted that this is the fourth and largest randomised phase III study of pirfenidone compared with placebo in idiopathic pulmonary fibrosis. Given the conflicting results observed between the PIPF-004 and PIPF-006 studies and that favourable results for pirfenidone were generally found only in the pooled analyses, the Committee recommended that pirfenidone's use for treating idiopathic pulmonary fibrosis should be reviewed by NICE once the ASCEND results are available in 2014.

Summary of Appraisal Committee’s key conclusions

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<th>TA282</th>
<th>Appraisal title: Pirfenidone for treating idiopathic pulmonary fibrosis</th>
<th>Section</th>
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<tr>
<td></td>
<td>Key conclusion</td>
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Pirfenidone is recommended as an option for treating idiopathic pulmonary fibrosis only if the person has a forced vital capacity (FVC) between 50% and 80% predicted and the manufacturer provides pirfenidone with the discount agreed in the patient access scheme. Treatment with pirfenidone should be discontinued if there is evidence of disease progression (a decline in per cent predicted FVC of 10% or more within any 12-month period).

The Committee concluded that pirfenidone seemed to have a modest but measurable effect on slowing the decline in lung function, but that there was uncertainty in whether this benefit persisted over time because of the lack of data on pirfenidone’s effect on lung function beyond 72 weeks of treatment.

The Committee agreed that the most plausible ICER was for the comparison of pirfenidone with best supportive care in people who had idiopathic pulmonary fibrosis with FVC 80% predicted or less, incorporating the second patient access scheme. It noted that the manufacturer’s probabilistic ICER was £24,000 per QALY gained. It concluded that this offered an acceptable cost-effectiveness estimate on which to begin to explore its further considerations. Because this ICER was within the range normally considered to represent a cost-effective use of NHS resources and was associated with an acceptable level of uncertainty, the Committee concluded that pirfenidone should be recommended for the treatment of idiopathic pulmonary fibrosis in people with FVC between 50% and 80% predicted.

Current practice
The Committee heard from clinical specialists that there may be variation in care depending on whether this is in a specialised centre or not and because of a lack of recognised care pathways in some parts of the country. It heard that current initial treatment options included N-acetylcysteine, observation and best supportive care and participating in a clinical trial. The Committee heard from patient experts that symptoms of idiopathic pulmonary fibrosis can have a debilitating effect and that patients would place high value on any new treatment that could prevent symptoms from worsening, decrease dependency on oxygen, increase survival and reduce hospitalisation.

The Committee heard from the clinical specialists that it would be preferable to use drugs that modify the natural history of the disease before irreversible damage occurs. The Committee acknowledged the challenges of treating idiopathic pulmonary fibrosis and recognised the need for new effective treatment options to inhibit disease progression.

<table>
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<tr>
<th>Clinical need of patients, including the availability of alternative treatments</th>
<th>The Committee heard from clinical specialists that there may be variation in care depending on whether this is in a specialised centre or not and because of a lack of recognised care pathways in some parts of the country. It heard that current initial treatment options included N-acetylcysteine, observation and best supportive care and participating in a clinical trial. The Committee heard from patient experts that symptoms of idiopathic pulmonary fibrosis can have a debilitating effect and that patients would place high value on any new treatment that could prevent symptoms from worsening, decrease dependency on oxygen, increase survival and reduce hospitalisation.</th>
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<th>The technology</th>
<th>Pirfenidone (Esbriet, InterMune) is an immunosuppressant that is thought to have anti-inflammatory and antifibrotic effects which are likely to be mediated by suppressing fibroblast proliferation, reducing the production of fibrosis-associated proteins and cytokines, and reducing the response to growth factors. The Committee concluded that pirfenidone seemed to have a modest but measurable effect on slowing the decline in lung function, but that there was uncertainty in whether this benefit persisted over time because of the lack of data on pirfenidone’s effect on lung function beyond 72 weeks of treatment. The Committee considered that pirfenidone had an innovative mechanism of action but that it could not be considered a step change in the management of idiopathic pulmonary fibrosis, given its modest effect observed over a short duration. The Committee concluded that there were no additional QALYs that had not been incorporated into the economic model and the cost-effectiveness estimates.</th>
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<tr>
<td>What is the position of the treatment in the pathway of care for the condition?</td>
<td>Pirfenidone has a UK marketing authorisation for the treatment of mild-to-moderate idiopathic pulmonary fibrosis in adults. The Committee recommended pirfenidone as an option for treating idiopathic pulmonary fibrosis in people with FVC between 50% and 80% predicted.</td>
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<tr>
<td>Adverse reactions</td>
<td>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. The Committee heard from the clinical specialists that the adverse effects were generally transient and usually resolved if the dose of pirfenidone was reduced or temporarily discontinued. The Committee concluded that pirfenidone's adverse-effect profile was acceptable in a severe disease such as idiopathic pulmonary fibrosis, but that it was also significant given the potential long-term administration of pirfenidone.</td>
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**Evidence for clinical effectiveness**

| Availability, nature and quality of evidence | The Committee noted that, although the study protocols stated secondary outcome variables should only be analysed using pooled data if the primary efficacy end points from each study were achieved, the European Medicines Agency had accepted the pooled analyses from PIPF-004 and PIPF-006. The Committee noted the near-identical design of PIPF-004 and PIPF-006 and agreed that analyses of the pooled data were reasonable. Overall, the Committee concluded that the trials provided evidence that was adequate for currently assessing the clinical effectiveness of pirfenidone in idiopathic pulmonary fibrosis. | 4.4 |
### Relevance to general clinical practice in the NHS

The Committee concluded that it was acceptable to consider the treatment given in the placebo arms of the clinical trials to be equivalent to best supportive care in UK clinical practice but noted an issue of generalisability because the full clinical trial population had milder idiopathic pulmonary fibrosis and fewer comorbidities than typically seen in UK clinical practice.

The Committee concluded that, although specified in the NICE scope, triple therapy was no longer routine or best practice in the NHS for patients starting treatment for idiopathic pulmonary fibrosis and could no longer be considered a comparator for pirfenidone.

### Uncertainties generated by the evidence

The Committee noted that PIPF-004, but not PIPF-006, met its primary outcome of a statistically significant difference in mean change in per cent predicted FVC at 72 weeks between the pirfenidone and placebo groups and that statistically significant differences between groups were detected for only 1 secondary outcome in each study. It agreed that any sustained benefit of pirfenidone was uncertain given the short duration of the efficacy data included in the manufacturer's submission and the differences between the results of PIPF-004 and PIPF-006. The Committee concluded that although it had concerns about the differences in the results of the 2 studies (particularly in relation to the outcomes considered important to people with idiopathic pulmonary fibrosis), the pooled analysis of the primary end point of PIPF-004 and PIPF-006 provided acceptable evidence of pirfenidone's overall modest treatment effect over a short duration.
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?

<table>
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<tr>
<th>The Committee heard from the clinical specialists that FVC 80% predicted or less was an arbitrary but acceptable threshold for initiating treatment for idiopathic pulmonary fibrosis and that this could be easily implemented in clinical practice. The Committee concluded that the subgroup of patients with FVC 80% predicted or less was clinically relevant and acceptable for making treatment decisions in clinical practice. The Committee concluded that although the estimates of effectiveness derived from the subgroup analyses based on the FVC predicted value were not statistically robust it was reasonable to consider the results of these analyses because the subgroup with FVC 80% predicted or less more closely reflected the population with idiopathic pulmonary fibrosis in England and Wales than the full trial population.</th>
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<td>4.14, 4.15</td>
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Estimate of the size of the clinical effectiveness including strength of supporting evidence

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<th>The Committee agreed that the 2.5% absolute difference in FVC decline at 72 weeks in the mild-to-moderate population could be considered clinically significant, but that a sustained benefit was uncertain given the short duration of PIPF-004 and PIPF-006 and the differences between the results of the 2 studies. The Committee concluded that although there was uncertainty about a possible survival benefit based on the data from PIPF-004 and PIPF-006 because of the small number of events and short follow-up, this was the only evidence available for decision-making.</th>
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<td>4.9, 4.12</td>
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Evidence for cost effectiveness

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<th>The Committee had reservations over the complexity and lack of transparency of the manufacturer's microsimulation model. The Committee concluded that the outlined structure of the model adhered to the NICE reference case for economic analysis and was acceptable for assessing the cost effectiveness of pirfenidone.</th>
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<td>4.16</td>
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<tr>
<td>Uncertainties around and plausibility of assumptions and inputs in the economic model</td>
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<tr>
<td>Incorporation of health-related quality-of-life benefits and utility values</td>
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</table>
### Are there specific groups of people for whom the technology is particularly cost effective?

The Committee was persuaded that the subgroup results from patients with FVC 80% predicted or less could be used to inform treatment decisions in UK clinical practice, and that this was the most appropriate population for evaluation. It noted that the manufacturer's probabilistic ICER was £24,000 per QALY gained, which was less than the ERG’s deterministic ICER for the mild-to-moderate population (the value is confidential).

### What are the key drivers of cost effectiveness?

The Committee discussed how uncertainty in the manufacturer's model had been explored in univariate sensitivity analyses by the manufacturer and the ERG. The Committee agreed with the manufacturer's conclusion that the ICERs were also sensitive to the discount rates for costs and outcomes as well as the daily dosage of pirfenidone. The Committee concluded that there was some uncertainty associated with the estimates of treatment effect of pirfenidone and mortality related to idiopathic pulmonary fibrosis, but that the level of uncertainty was acceptable for decision-making.

### Most likely cost-effectiveness estimate (given as an ICER)

The Committee was persuaded that the subgroup results from patients with FVC 80% predicted or less was the most appropriate population for evaluation. It considered that triple therapy was no longer routine or best practice in the NHS for patients starting treatment for idiopathic pulmonary fibrosis, and so best supportive care should be considered the sole comparator for pirfenidone. The Committee therefore agreed that the most plausible ICER was for the comparison of pirfenidone with best supportive care in people who had idiopathic pulmonary fibrosis with FVC 80% predicted or less, incorporating the second patient access scheme. It was persuaded that the manufacturer's probabilistic ICER was £24,000 per QALY gained. It concluded that this offered an acceptable cost-effectiveness estimate on which to begin to explore its further considerations.

### Additional factors taken into account

**Patient access schemes (PPRS)**

The manufacturer agreed a patient access scheme with the Department of Health in which a simple confidential discount is applied to the list price of pirfenidone.

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### End-of-life considerations

The Committee heard from the clinical specialists that life expectancy for patients with mild-to-moderate idiopathic pulmonary fibrosis would typically exceed 2 years. Having established that pirfenidone did not meet the criterion for short life expectancy, the Committee decided it was not necessary to make a decision about the population or extension to life criteria. The Committee concluded that pirfenidone did not fulfil the criteria to be considered as a life-extending, end-of-life treatment.

### Equalities considerations and social value judgements

The Committee noted that it was raised at consultation that idiopathic pulmonary fibrosis predominantly affects older people. Because its recommendation applied equally to all people with idiopathic pulmonary fibrosis, regardless of age, the Committee concluded that its decision on the use of pirfenidone would not have a particular impact on older people and that there was no need to alter or add to its recommendations.
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 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph 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.

5.3 The Department of Health and the manufacturer have agreed that pirfenidone will be available to the NHS with a patient access scheme which makes pirfenidone available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the manufacturer 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 global.pas@roche.com (01707 366000).

5.4 NICE has developed tools to help organisations put this guidance into practice (listed below).

- Costing template and report to estimate the national and local savings and costs associated with implementation.
6  Recommendations for further research

6.1  The Committee acknowledges the ongoing ASCEND study comparing pirfenidone with placebo in patients with idiopathic pulmonary fibrosis. The Committee recommends that data from this study should be considered in any review of this guidance.
7 Related NICE guidance

Details are correct at the time of publication. Further information is available on the NICE website.

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).
8 Review of guidance

8.1 The guidance on this technology will be considered for review within 6 months of publication of the results of the ASCEND study (expected in 2014). The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon
Chief Executive
April 2013
9 Appraisal Committee members, guideline representatives and NICE project team

A Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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.

Professor Peter Clark (Chair)
Consultant Medical Oncologist, Clatterbridge Centre for Oncology

Professor Jonathan Michaels (Vice Chair)
Professor of Clinical Decision Science, University of Sheffield

Professor Darren Ashcroft
Professor of Pharmacoepidemiology, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Dr Aomesh Bhatt
Regulatory and Medical Affairs Director Europe and North America, Reckitt Benckiser

Dr Andrew Black
General Practitioner, Mortimer Medical Practice, Herefordshire

Dr Matthew Bradley
Therapy Area Leader, Global Health Outcomes, GlaxoSmithKline
Professor John Hutton  
Professor of Health Economics, University of York

Professor Peter Jones  
Emeritus Professor of Statistics, Keele University

Dr Steven Julious  
Reader in Medical Statistics, University of Sheffield

Dr Tim Kinnaird  
Lead Interventional Cardiologist, University Hospital of Wales, Cardiff

Rachel Lewis  
Advanced Nurse Practitioner, Manchester Business School

Professor Femi Oyebode  
Professor of Psychiatry and Consultant Psychiatrist, The National Centre for Mental Health

Dr John Radford  
Director of Public Health, Rotherham Primary Care Trust and MBC

Dr Phillip Rutledge  
GP and Consultant in Medicines Management, NHS Lothian

Dr Brian Shine  
Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford

Dr Murray Smith  
Associate Professor in Social Research in Medicines and Health, University of Nottingham

Paddy Storrie  
Lay Member

Charles Waddicor  
Chief Executive, NHS Berkshire West


**B Guideline representatives**

The following individuals, representing the Guideline Development Group responsible for developing NICE’s clinical guideline related to this topic, were invited to attend the meeting to observe and to contribute as advisers to the Committee.

- Dr Nik Hirani – Chair of the Guideline Development Group

**C 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.

Linda Landells  
Technical Lead

Bhash Naidoo  
Technical Adviser

Rebecca Pye  
Project Manager
10  Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by Southampton Health Technology Assessment Centre:

- Cooper K, Mendes D, Picot J et al. Pirfenidone for the treatment of idiopathic pulmonary fibrosis: A single technology appraisal, February 2012

B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- InterMune

II Professional/specialist and patient/carer groups:

- Association for Respiratory Technology and Physiology
- British Lung Foundation
- British Thoracic Society
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- South Asian Health Foundation

III Other consultees:

- Berkshire East Teaching PCT
- Department of Health
- Welsh Government
IV Commentator organisations (did not provide written evidence and without the right of appeal):

- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- HealthCare Improvement Scotland
- MRC Clinical Trials Unit
- National Clinical Guidelines Centre
- National Institute for Health Research Health Technology Assessment Programme
- Southampton Health Technology Assessment Centre

C The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They gave their expert personal view on pirfenidone by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Melissa Hippard, nominated by National Clinical Guidelines Centre – patient expert
- Dr Toby Maher, nominated by British Thoracic Society and InterMune – clinical specialist
- Dr Srikumar Mallik, nominated by South Asian Health Foundation – clinical specialist
- Dr Lisa Spencer, nominated by British Thoracic Society and InterMune – clinical specialist
- Malcolm Weallans, nominated by National Clinical Guidelines Centre – patient expert

D Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- InterMune
About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE single technology appraisal process.

We have produced a summary of this guidance for patients and carers. Tools to help you put the guidance into practice and information about the evidence it is based on are also available.

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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