Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Professor Angela Timoney FRPharmS
NHS SCOTLAND

pirfenidone 267mg capsule (Esbriet®) SMC No. (835/13)

InterMune

05 July 2013

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a resubmission

pirfenidone (Esbriet®) is accepted for restricted use within NHS Scotland.

Indication under review: In adults for the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF).

SMC restriction: For use in patient with a predicted forced vital capacity (FVC) less than or equal to 80%.

Pirfenidone reduced the decline in lung function parameters associated with IPF compared to placebo in a pooled analysis of two similarly designed phase lll studies.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of pirfenidone. This SMC advice is contingent upon the continuing availability of the Patient Access Scheme in NHS Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 12 August 2013

Indication

In adults for the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF).

Dosing Information

One capsule three times a day for one week, then two capsules three times a day for one week, then three capsules three times a day thereafter. Capsules should be swallowed whole with water and taken with food to reduce the possibility of nausea and dizziness. Treatment with pirfenidone should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of IPF.

Product availability date

May 2013

Pirfenidone was designated as an orphan medicine on 16 November 2004

Summary of evidence on comparative efficacy

Idiopathic pulmonary fibrosis (IPF) is a rare disease characterised by progressive fibrosis of the lung interstitium, resulting in reduced lung volume and progressive pulmonary insufficiency. The median survival after diagnosis is approximately two to five years and death is due to respiratory failure in most patients. Pirfenidone, which is designated as an orphan medicinal product for the treatment of IPF, is the first medicine to be licensed for this condition.[1] Its mechanism of action is not fully established, but it is classified as an immunosuppressant. Pirfenidone attenuates fibroblast proliferation, production of fibrosis-associated proteins and cytokines, while increasing biosynthesis of extracellular matrix in response to cytokine growth factors such as transforming growth factor-beta and platelet-derived growth factor.[2]

The submitting company has requested that the Scottish Medicines Consortium (SMC) considers this product when positioned for use in patients with a predicted forced vital capacity (FVC) ≤80%.

Two very similar double-blind, phase lll studies (PIPF-004 and PIPF-006; also known as CAPACITY-2 and CAPACITY-1, respectively) recruited patients aged 40 to 80 years with a diagnosis of IPF in the previous 48 months, no improvement in disease severity over the preceding year, predicted FVC of at least 50%, predicted carbon monoxide diffusing capacity (DLco) of at least 35%, either predicted FVC or DLco less than 90% and six-minute walking test distance (6MWD) of at least 150m. They were randomised equally to placebo or pirfenidone 801mg orally three times daily, with an initial two-week dose titration, with treatment continued for all patients until 72 weeks after the last patient enrolled. The primary outcome, change from baseline to week 72 in percent-predicted FVC, was assessed in the intention-to-treat population, which included all randomised patients who received any study treatment, by a ranked analysis of covariance. In the CAPACITY-2 study, mean reduction in percent-predicted FVC from baseline to week 72 was significantly less with pirfenidone daily compared to placebo, 8% versus 12.4%. In the CAPACITY-1 study, there was no significant difference between pirfenidone and placebo in mean reduction of percent-predicted FVC from baseline to week 72, 9% versus 9.6%. In an analysis of data pooled from these studies, mean reduction in percent-predicted FVC from baseline to week 72 was significantly less with pirfenidone compared to

placebo, 8.5% versus 11%.[1,3-5] The absolute difference in the median percent-predicted FVC was the same in both studies, -1.1.[1] A post-hoc analysis of the pooled data in the subgroup with baseline predicted FVC ≤80% indicated that mean reduction from baseline to week 72 in percent-predicted FVC was significantly less with pirfenidone compared to placebo.[6]

Pirfenidone significantly reduced the mean decline in 6MWD from baseline to week 72 compared to placebo, a secondary outcome, in the CAPACITY-1 study and in the pooled analysis but not in the CAPACITY -2 study. Details are presented in Table 1.[1,3-5] To support the proposed positioning, an analysis of pooled data from both studies within the subgroup of patients with percent-predicted FVC ≤80%, found the decrease from baseline at week 72 in 6MWD was significantly lower in the pirfenidone group compared to placebo.

Table 1: change from baseline to week 72 in percent-predicted forced vital capacity (FVC) and 6 minute walking test distance (6MWD)[1,3-5]

			Decline from baseline to week 72	
		N	**FVC, (%)**	**6MWD, (meters)**
CAPACITY-2	Pirfenidone	174	8.0	60
	Placebo	174	12.4	77
CAPACITY-1	Pirfenidone	171	9.0	45
	Placebo	173	9.6	77
CAPACITY-1 and 2 pooled	Pirfenidone	345	8.5	53
	Placebo	347	11	77

In pooled exploratory analyses of all available data to the end of the CAPACITY-1 and 2 studies, there were no significant differences between pirfenidone and placebo in overall mortality or in IPF-related mortality. In similar analyses using 'on-treatment' data from randomisation until 28 days after last dose of study drug, there was no significant difference between pirfenidone and placebo in overall mortality. However, there was a significant reduction in IPF-related mortality with pirfenidone compared to placebo.[1,3-5] Details are presented in Table 2.

Table 2: all-cause and IPF-related mortality overall and on-treatment

Mortality		**CAPACITY-1 and 2 pooled**	
		Pirfenidone	**Placebo**
Overall	**All-cause**	7.8% (27/345)	9.8% (34/347)
HR (95%CI)		0.77 (0.47 to 1.28)	
Overall	**IPF-related**	5.2% (18/345)	8.1% (28/347)
HR (95%CI)		0.62 (0.35 to 1.13)	
On-treatment	**All-cause**	5.5% (19/345)	8.4% (29/347)
HR (95%CI)		0.65 (0.36 to 1.16)	
On-treatment	**IPF-related**	3.5% (12/345)	7.2% (25/347)
HR (95%CI)		0.48 (0.24 to 0.95)	

HR=Hazard ratio CI=confidence interval

In the exploratory analyses of pooled data from CAPACITY 1 and 2 within the subgroup of patients with percent-predicted FVC ≤80%, pirfenidone 2403mg was associated with significant reductions from placebo in overall all-cause and IPF-related mortality; in on-treatment all-cause and IPF-related mortality; and in IPF-related mortality using data up to week 72, HR 0.35.

In post-hoc analyses of the pivotal studies both separately and pooled, the number of hospitalisations for respiratory and non-respiratory reasons were similar in the pirfenidone and placebo groups; however, the mean duration of hospital stay was shorter in the pirfenidone group compared to the placebo group for both respiratory hospitalisations (8.0 vs. 14.6 days, respectively, in the pooled analysis) and non-respiratory hospitalisations (8.8 vs. 18.0 days, respectively, in the pooled analysis).

An open-label extension of the CAPACITY-1 and 2 studies, RECAP (PIPF-012), included 77% (603/779) of the originally randomised patients: 261 had initially been randomised to pirfenidone 2403mg daily, 68 to pirfenidone 1197mg daily and 274 to placebo. All patients were treated with pirfenidone 2403mg daily. [6] This extension primarily assessed safety but efficacy was a secondary objective. In a separate analysis of RECAP, at week 60, the mean change in percent-predicted FVC in patients previously treated with placebo was similar to that achieved in the original pooled analysis of the CAPACITY studies.

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

Adverse effects associated with pirfenidone appear to be generally mild to moderate in severity, dose-related and reversible, with gastro-intestinal and skin disorders being the most common. In pooled data from the CAPACITY-1 and 2 studies, incidences of the most common adverse events in the respective pirfenidone 2403mg and placebo groups were nausea (36% and 17%), rash (32% and 12%), dyspepsia (19% and 7%), dizziness (18% and 10%), vomiting (14% and 4%), photosensitivity reaction (12% and 2%) and anorexia (11% and 4%). Rates of serious adverse events were comparable between the respective groups: 33% and 31%. Discontinuation due to adverse events occurred more frequently in the pirfenidone group 15% versus 9%, mainly due to gastro-intestinal and skin events.[1,3-5]

*Other data were also assessed but remain commercially confidential.**

Summary of clinical effectiveness issues

IPF is a heterogeneous collection of idiopathic conditions which manifest as pulmonary fibrosis making response to treatment difficult to predict. Prognosis is poor and, following diagnosis, survival is estimated at 2 to 5 years.[1]

The main approach to treatment of IPF within NHS Scotland is best supportive care. In the recent past, some patients with IPF received triple therapy with azathioprine, prednisolone and N-acetylcysteine. However, an interim analysis of the PANTHER study indicated that this regimen was associated with significantly greater morbidity and mortality relative to placebo, and based on this, the British Thoracic Society (BTS) issued advice in 2011 that new patients with IPF should not be initiated on a regimen containing prednisolone plus azathioprine. SMC

clinical experts have advised that triple therapy is unlikely to be used and that some patients receive N-acetylcysteine and/or low dose corticosteroid. An unmet need in respect of any effective treatment for IPF was identified by clinical experts. The potential place of pirfenidone in clinical practice relative to other treatments is unclear.

There is ongoing debate about the most appropriate outcome for use in the investigation of IPF, with at present no validated surrogate endpoints and no threshold for clinically significant changes in measures of lung function, such as FVC. However, the European Medicines Agency (EMA) concluded that percent-predicted FVC is a well-recognised measure of disease progression and prognosis in IPF[1] and a recent editorial concluded that trends in FVC reliably predict mortality in IPF and is the best indicator of chronic disease progression, although not proven as a surrogate for mortality. [7]

Pirfenidone is the first medicine to be licensed for the treatment of IPF. The submitting company has requested that the SMC considers this product when positioned for use in patients with a percent-predicted FVC ≤80%.

Pooled analysis of the two pivotal studies demonstrated a statistically significant reduction in the primary outcome of change in percent-predicted FVC from baseline to week 72. However the results were not consistent across the two studies, with a significant difference for pirfenidone compared with placebo demonstrated in study CAPACITY-2, but not in the almost identical, CAPACITY-1 study. The clinical significance of the treatment effect relative to placebo for mean reduction in percent-predicted FVC (4.4% in study CAPACITY-2 and 2.5% in the pooled analysis) is uncertain.

Following post hoc analysis, the failure of the CAPACITY-1 study to detect a significant difference for pirfenidone over placebo has been attributed to a reduced rate of decline of FVC in the placebo group. It has been suggested that this may be due to a higher proportion of patients in the placebo group with more obstructive physiology which is associated with less decline in lung function.[3] The mixed results across the two studies is further confounded by a significant benefit for pirfenidone over placebo for the secondary outcome of reduction in the mean decline in 6MWT reported in the CAPACITY-1 study but not in the CAPACITY-2 study.[3] Therefore, there is uncertainty around the size of benefit that will be achieved in clinical practice. In addition, generalisability of the study results to the Scottish population is uncertain as patients in the clinical studies had few co-morbidities and other concomitant therapies for IPF were prohibited.

The primary outcome in patients with a percent-predicted FVC ≤80% comes from a post hoc analysis of the pooled results from the two pivotal studies. This demonstrated a significant treatment effect for pirfenidone over placebo, but the study was not powered for this analysis.

The studies were not powered to investigate effects on mortality and these analyses were exploratory, based on observational data.[1] Although the pooled analysis indicated an effect on IPF-related mortality, this is limited by some uncertainty in the assignment of cause of death and whether this was IPF-related. However, the survival benefit in terms of all-cause mortality in analysis of the subgroup with FVC≤80% would not be compromised by the lack of adjudication and inconsistencies in data handling. These indicated HR of 0.56 and 0.44 for overall and on-treatment mortality, respectively. Data to support the long term benefit of pirfenidone for up to four years is based on an open label safety study providing a Kaplan Meier estimate of survival up to 132 weeks.

In the CAPACITY-1 study, the primary outcome measure was significant from week 12 to 48, but not at weeks 60 and 72, possibly suggesting a diminishing treatment effect over time. It is therefore possible that the duration of the studies is not adequate to characterise fully the treatment effects of pirfenidone, leading to uncertainty around if and when to discontinue treatment and the parameters used to make the decision. The EMA refers to the section on 'Length of Treatment' in the ATS/ERS joint statement[16] and concludes that therapy should be continued indefinitely only in patients with objective evidence of continued improvement or stablisation.[3] In clinical practice, it may be useful to define criteria for discontinuing treatment when it is considered to be no longer having an effect.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing pirfenidone with best supportive care (BSC) for the treatment of IPF in a sub-population of patients with FVC ≤80%. The time horizon was 18.5 years, equivalent to 40 cycles of the model.

The primary source of clinical evidence used was 72 week pooled patient level data from the sub-population with FVC ≤80% from the CAPACITY-1 and 2 studies of pirfenidone versus placebo. A microsimulation model with a cycle length of 24 weeks was used to estimate the outcomes of IPF-related mortality, all cause hospitalisation and health related quality of life scores as measured by the SGRQ. Using the placebo data from the CAPACITY-1 and 2 studies, a series of regressions were developed to estimate the relationship between these outcomes and FVC and the 6MWD test outcomes as independent predictors. An adjustment factor was applied to the regression for mortality in order to calibrate the model predictions for survival with those directly derived from the pooled CAPACITY-1 and 2 studies. The results from the regressions were then applied to the coupled FVC and 6MWD values for the pirfenidone and placebo arms to estimate a per cycle hazard ratio for IPF related mortality, a per cycle probability of hospitalisation and impact on SGRQ score.

Utilities were estimated using a de novo algorithm for mapping between the SGRQ and EQ- 5D that used data from a clinical study containing patients with IPF. The costs of pirfenidone were based on the estimated number of capsules per day derived from the PIPF-004 and PIPF-006 studies, with estimated discontinuation rates also derived from the same source. No adverse event costs were estimated on the grounds that these would be negligible. In terms of resource use, the use of oxygen therapy and patient monitoring (outpatient visits, tests) were included with this estimated via the use of clinical expert opinion. Hospitalisation costs were based on an estimated length of stay derived from the CAPACITY-1 and 2 studies for pirfenidone and placebo arm patients with FVC≤80%. In addition, one-off end of life costs were also estimated based on a published study of patients with respiratory and heart failure. Unit costs were from recognised published sources and discounting was applied at 3.5% for costs and benefits.

A patient access scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a confidential discount was offered on the price of the medicine. The base case result with the PAS was an incremental cost effectiveness ratio (ICER) of £27,575 per quality adjusted life year (QALY) gained.

The primary driver of benefit for pirfenidone is the reduced IPF related mortality estimated for pirfenidone.

A range of sensitivity and scenario analyses were performed. Varying utilities by adjusting the inputs to the mapping equations ±20% resulted in an ICER range of £23.7k - £34.4k/QALY with PAS. The most sensitive cost variable in one way sensitivity analysis was the number of capsules taken per day. If length of stay for hospitalisations were assumed to be the same for both arms of the model, the ICER increased to £32.6k/QALY. Using the trial based confidence intervals for the 72 week hazard ratio resulted in an ICER with PAS ranging from £24.9k/QALY with the lower CI (0.16) to £36.3k/QALY with the upper CI (0.74). Applying the regression based result for mortality without an adjustment to calibrate with the trial based HR produced an estimated £42.7k/QALY gained. Other cost and structural parameters did not have a large impact on the ICER.

There were a number of weaknesses and limitations with the comparison with BSC:

- There is general uncertainty about the benefits of pirfenidone over the longer term duration of the model given that the studies were not powered to investigate the effects on mortality and the data provided are exploratory and based on observational data. As noted above, the ICERs show sensitivity to changes in the parameters driving survival gains (range of £24.9k/QALY to £36.3k/QALY)
- The reliability of the IPF-related mortality data from the CAPACITY 1 and 2 studies has been questioned. It may have been preferable to use all-cause mortality in the economic analysis as it is not subject to the problems with the reliability of IPF related mortality in the clinical studies. All-cause mortality also shows statistical significance for pirfenidone vs placebo in the CAPACITY 1 and 2 pooled trials in the sub-population with FVC ≤80%. Sensitivity analysis using all cause mortality data increased the with- PAS ICER to £29,218.
- The simulation model with outcomes predicted via linear regression analysis poorly predicted IPF-related mortality outcomes. The calibration with trial data was useful, but the long run mortality estimates were based on an assumption of proportional hazards which may not be realistic. Hence, overall there is uncertainty in the survival benefits estimated. The fitting of parametric curves to the CAPACITY 1 and 2 data would have been useful, although the submitting company claimed this was attempted but did not produce meaningful results.
- Given the survival prognosis of patients with IPF, a shorter time horizon of 10 years increased the ICER slightly to £29,391 per QALY.
- The utility estimates used were based on an SGRQ to EQ-5D mapping function which had reasonably low predictive strength, even when data from IPF patients were used. The ICERs showed some sensitivity to changing the inputs to the mapping functions ranging up to £34,363 per QALY.
- The unit costs of hospitalisation were based on clinical trial data without verification of generalisability to Scottish clinical practice. If no differences in length of stay were assumed between pirfenidone and placebo patients, the ICER increased to £32,644
- The costs and benefits of lung transplantation were not considered in the base case. However, the company did provide some additional analysis to show the impact of including transplants in the model and this resulted in an ICER of £28,337 (using all cause mortality data).
- The analysis did not incorporate any stopping rules and it would have been useful to see the impact on the results from such an inclusion. The company provided additional

sensitivity analysis to model stopping rules. This was presented around a base case that used all cause mortality and included an allowance for transplants. This resulted in ICERs of £28,164, £28,631 and £28,883 for stopping rules based on EPAR criteria, a 6 month or 12 month stopping rule respectively.

SMC considered the likely range of cost-effectiveness ratios for pirfenidone and the remaining uncertainties in the economic case. The committee considered the benefits of pirfenidone in the context of the SMC modifiers and agreed that two of the criteria were met: evidence of an improvement in life expectancy in the patient population targeted in the submission; and absence of other therapeutic options of proven benefit for the disease in question.

In light of this, the economic case was considered demonstrated.

It is SMC policy to include the estimated QALY gain in the detailed advice document for all submissions. The PAS for pirfenidone includes a discount to the NHS that is commercial in confidence and the submitting company has advised that publication of the QALY gain, when considered with other cost-effectiveness data in the public domain, could reveal the level of discount. For this reason SMC is unable to publish the estimated QALY gain.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

A Patient Interest Group Submission was received from the Pulmonary Fibrosis Trust.

Additional information: guidelines and protocols

In 2008 the BTS in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society issued an interstitial lung disease guideline. This noted that best supportive care should be considered a specific and important treatment strategy in all patients with IPF. It is a proactive approach to symptomatic treatment and may include oxygen therapy, pulmonary rehabilitation, opiates, antireflux therapy, withdrawal of steroids and other immunosuppressants, early recognition of terminal decline and liaison with palliative care specialists. To date there is no therapy proven to improve survival or otherwise significantly modify the clinical course of IPF. As such, it is recommended that all patients be considered for recruitment to high quality clinical trials of therapy and/or for lung transplantation if appropriate. Prednisolone (tapering from 0.5mg/day to 10-20mg/day) with azathioprine (2mg/kg, maximum 150mg/day) and N-acetylcysteine (600mg three times a day) has been shown to have a significantly better treatment effect than prednisolone and azathioprine alone. However, further studies are required and this regimen currently carries a weak recommendation.[8] The BTS issued an update in November 2011 in response to the discontinuation of the triple-therapy arm of the PANTHER study when an interim analysis indicated increased morbidity and mortality compared to placebo. This recommends that new patients with definite IPF should not be initiated on a regimen containing prednisolone plus azathioprine. In patients with definite IPF already receiving combination prednisolone, azathioprine and N-acetylcysteine therapy, it is recommended that azathioprine therapy in particular should be withdrawn if there is evidence of disease progression (declining lung function). In patients established on triple therapy with

'stable' disease, the decision to withdraw should be on a case-by-case basis, but the threshold for withdrawing azathioprine from elderly patients should be low.

In 2011 an official statement was issued by the American Thoracic Society (ATS), the European Respiratory Society (ERS), the Japanese Respiratory Society (JRS) and the Latin American Thoracic Association (ALAT) on idiopathic pulmonary fibrosis: evidence based guidelines for diagnosis and management. This notes that the committee felt that the preponderance of evidence to date suggests that pharmacologic therapy for IPF is without definitive, proven benefit and makes recommendations of varying strengths against most therapies. The recommendation against the use of the following drugs is strong: corticosteroid monotherapy, colchicine, cyclosporine A, combined corticosteroid and immune-modulator therapy, interferon, bosentan and etanercept. The recommendation against the use of the following is weak, that is these therapies should not be used in the majority of patients with IPF, but may be a reasonable choice in the minority: combined N-acetylcysteine, azathioprine and prednisolone, N-acetylcysteine monotherapy, anticoagulation and pirfenidone.[9]

Additional information: comparators

There are no medicines licensed for treatment of IPF. The main current treatment is mainly best supportive care with some patients receiving off-label N-acetylcysteine and/or low dose corticosteroid

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Pirfenidone	**801mg three times daily**	**26,100**
N-acetylcysteine	600mg three times daily	243

Additional information: budget impact

The submitting company presented two scenarios using different prevalence rates to calculate the budget impact. The different prevalence rates were taken from two different reports:

Scenario 1
The submitting company estimated the population eligible for treatment to be 792 in year 1 rising to 806 in year five with an estimated uptake rate of 13.5% in year 1 and 18.9% in year 5.

Without PAS: The gross impact on the medicines budget was estimated to be £2.049m in year 1 and £2.919m in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be £2.041m in year 1 and £2.915m in year 5.

Scenario 2
The submitting company estimated the population eligible for treatment to be 624 in year 1 rising to 633 in year five with an estimated uptake rate of 13.5% in year 1 and 18.9% in year 5.

Without PAS: The gross impact on the medicines budget was estimated to be £1.613m in year 1 and £2.293m in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be £1.607m in year 1 and £2.291m in year 5.

Comments received from SMC clinical experts suggest that the levels of uptake predicted by the company may be conservative.

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission.

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3. Noble PW, Albera C, Bradford WZ et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet 2011; 377: 1760-9.
4. Food and Drug Administration. Briefing Information for the March 9, 2010 Meeting of the Pulmonary-Allergy Drugs Advisory Committee: Overview of the FDA background materials for New Drug Application (NDA) 22-535, Esbriet (pirfenidone) for the treatment of patients with idiopathic pulmonary fibrosis (IPF) to reduce the decline in lung function
5. InterMune. Briefing Information for the March 9, 2010 Meeting of the Pulmonary-Allergy Drugs Advisory Committee.
6. Costabel U., Albera C., Bradford W et al. Analysis of lung function and survival in RECAP: An open-label extension study of pirfenidone (PFD) in patients with idiopathic pulmonary fibrosis (IPF). Ruhrlandklinik, Essen, Germany, 2012.
7. Wells AU. Forced vital capacity as a primary endpoint in idiopathic pulmonary fibrosis treatment trials: making a silk purse out of a sow's ear. Thorax 2013:68;309-310
8. Wells AU, Hirani N. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Thorax 2008; 63 Suppl 5: v1-58.
9. Raghu G, Collard HR, Jim J et al. An official ATS/ERS/JRS/ALAT Statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011; 183: 788-24.

This assessment is based on data submitted by the applicant company up to and including 14 June 2013.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of

guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.