

**7.09 PIRFENIDONE,
267 mg Capsule, 270,
Esbriet[®],
Roche Products Pty Ltd.**

1 Purpose of Application

1.1 Resubmission to request Section 100 (Highly Specialised Drugs (HSD) Program) Authority Required listing for treatment of idiopathic pulmonary fibrosis (IPF).

2 Requested listing

2.1 An abbreviated version of the requested restriction is below. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough in the following abbreviated version.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
PIRFENIDONE Capsules 267 mg, 270	1	5	Public hospital: \$ [REDACTED] (effective price: \$ [REDACTED]) Private hospital: \$ [REDACTED] (effective price: \$ [REDACTED])	Esbriet [®] Roche Products Pty Ltd

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Idiopathic pulmonary fibrosis
PBS Indication:	Idiopathic pulmonary fibrosis
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required – Telephone
Treatment phase:	Initial treatment
Treatment criteria:	Patient Must be treated by a respiratory physician or specialist physician experienced with expertise in the management of patients with idiopathic pulmonary fibrosis, OR <i>Must be treated by a specialist physician with expertise in the management of idiopathic pulmonary fibrosis</i> AND <i>Must be treated in a centre with expertise in idiopathic pulmonary fibrosis, OR</i> <i>Must be treated in consultation with a centre with expertise in idiopathic pulmonary fibrosis if attendance is not possible due to geographic isolation.</i>

Public Summary Document – November 2016 PBAC Meeting

Clinical criteria:	<p>Patient must have confirmed diagnosis of idiopathic pulmonary fibrosis. AND Patient must have chest high resolution computed tomography (HRCT) with surgical lung biopsy consistent with the diagnosis of idiopathic pulmonary fibrosis, OR Patient must have chest high resolution computed tomography (HRCT) without surgical lung biopsy consistent with the diagnosis of idiopathic pulmonary fibrosis, AND Patient must have percent predicted forced vital capacity (FVC) equal to or greater than 50% for age, gender and height weight, and forced expiratory volume in 1 second (FEV1)/FVC ratio greater than 0.7, AND Patient must have <i>diffusing capacity of the lungs for percent predicted carbon monoxide</i> diffusing capacity (DLCO) corrected for haemoglobin equal to or greater than 30%. AND <i>The treatment must not be in combination with PBS-subsidised nintedanib.</i></p>
Population criteria:	Patient must be aged 40 years or older.
Prescriber Instructions	<p>Consultation with a multidisciplinary team is necessary in the diagnosis of idiopathic pulmonary fibrosis (IPF). The multidisciplinary team may comprise of at least a pulmonologist, radiologist and where required, pathologist.</p> <p>Authority applications for initial treatment must be made in writing and must include:</p> <ul style="list-style-type: none"> (a) a completed authority prescription form; and (b) a completed IPF Initial PBS authority application form which includes: <ul style="list-style-type: none"> (i) a copy of the high-resolution computed tomographic scan results with or without surgical lung biopsy results confirming the diagnosis of IPF (ii) a copy of the respiratory function test results showing Forced Vital Capacity (FVC) equal to or greater than 50% <p>AND</p> <ul style="list-style-type: none"> (iii) a copy of the percent predicted <i>diffusing capacity of the lungs for carbon monoxide</i> diffusing capacity (DLCO) corrected for haemoglobin equal or greater than 30%, and <p>(c) a signed patient acknowledgement;</p>

Treatment phase:	Continuing treatment
Category / Program	Section 100 – Highly Specialised Drugs Program (Community Access)
Treatment criteria:	<As per initial treatment>
Clinical criteria:	<p>Patient must have previously received PBS subsidised treatment with this drug for <i>this condition</i>. AND <i>The treatment must not be in combination with PBS-subsidised nintedanib.</i></p>
Population criteria:	Patient must be aged 40 years or older.

Public Summary Document – November 2016 PBAC Meeting

Treatment phase:	Initial PBS-subsidised treatment (grandfather patient)
Category / Program	Section 100 – Highly Specialised Drugs Program
Treatment criteria:	<As per initial treatment>
Clinical criteria:	Patient must have <i>previously</i> received non-PBS subsidised treatment with this drug <i>for this condition</i> prior to [listing date] AND <i>The treatment must not be in combination with PBS-subsidised nintedanib.</i>
Population criteria:	Patient must be aged 40 years or older.
Prescriber Instructions	<As per initial treatment>

- 2.2 The current resubmission sought listing on the basis of a cost utility analysis (CUA) comparing pirfenidone to best supportive care (BSC). As in the March 2016 minor resubmission, the current resubmission proposed a special pricing arrangement (SPA) with effective DPMQs of \$ [REDACTED] for public hospital and \$ [REDACTED] for private hospital under Section 100 (HSD). The equivalent effective DPMQ if recommended as a General Schedule (Section 85) listing would be \$ [REDACTED].
- 2.3 In November 2015, the PBAC requested that a future resubmission should explore the cost effectiveness of a stopping rule in restricting use of pirfenidone to patients likely to receive the most benefit. In March 2016, the sponsor proposed a [REDACTED]% rebate on the published price with the intention of improving the cost effectiveness to ensure a stopping rule would not be required. In its consideration of the March 2016 minor resubmission, the PBAC considered that implementing a stopping rule for pirfenidone would be difficult in clinical practice (March 2016 PSD, paragraph 5.2). The Pre-Sub-Committee Response (PSCR) (p2) stated that it would be clinically unjustifiable to impose a stopping rule when robust evidence exists supporting continued treatment, and no evidence exists to support discontinuation at a defined point of the disease course. The ESC considered that it may be preferable to manage the risk of continuing treatment with pirfenidone in patients who have experienced a significant decline in lung function through other methods (e.g. a risk sharing arrangement (RSA)).
- 2.4 The resubmission and the PSCR (p2) justified the request for listing under Section 100 (HSD) for the following reasons:
- Pirfenidone is a medicine for the treatment of a chronic condition, which requires access to specialist facilities to ensure accurate diagnosis.
 - IPF is an analogous clinical condition to pulmonary arterial hypertension (PAH); PAH treatments (including; ambrisentan, bosentan monohydrate, epoprostenol sodium, iloprost trometamol, macitentan, sildenafil citrate, and tadalafil) are listed as Section 100 (HSD). The current resubmission noted that contrary to the Section 100 listings for PAH agents, the resubmission only proposed that the initial pirfenidone prescription needs to be under the affiliation of a specialist hospital unit, following the accurate IPF diagnosis via a multi-disciplinary team. Continuing treatment is proposed to be through the Section 100 HSD Community Access program.
 - A listing under the Section 100 (HSD) program improves the cost-effectiveness of pirfenidone and reduces the total cost to Government due to lower mark-ups and

Public Summary Document – November 2016 PBAC Meeting

fees. The ESC disagreed with this justification, noting that the program should be chosen on the basis of the appropriate mechanism for patients and prescribers. Given that administration of pirfenidone within a hospital setting is not required, the ESC considered that listing on the General Schedule may be more appropriate.

- 2.5 The PSCR (p1) requested that the clinical criterion which states a high resolution computed tomography (HRCT) consistent with the diagnosis of IPF is required be replaced with the requirement for a diagnosis consistent with IPF through a multidisciplinary team meeting. The PSCR argued that HRCT may have inaccurate or inconclusive results which may result in patients requiring repeat scans. The ESC agreed that the requirement for a multidisciplinary team was appropriate, noting that this may partly address the risk of leakage to other interstitial lung diseases, but considered this should be in addition to the requirement for HRCT consistent with the diagnosis of IPF.
- 2.6 The pre-PBAC response (p1), Australian Pulmonary Fibrosis Consortium and Australian IPF Registry Steering Committee (agenda item 14.13 refers) noted the importance of a clear diagnosis of IPF within the setting of an established specialist multidisciplinary team meeting for increased accuracy in diagnosis. The Australian IPF Registry further advised that the multidisciplinary team should be defined as a respiratory physician, radiologist and, where histological material is considered, a pathologist.
- 2.7 The Australian IPF Registry steering committee also advised that:
- the criterion specifying that the patient must be treated by a respiratory/specialist physician with expertise in the management of IPF be removed, given the absence of a definition of expertise; and
 - the requirement for HRCT scan results confirming diagnosis of IPF be removed and replaced with a requirement for evidence that a HRCT scan has been performed.
- 2.8 The ESC considered that it may be appropriate to include an additional note or criterion specifying that the patient must not have interstitial lung disease due to other known causes including domestic and occupational environmental exposures, connective tissue disease, and drug toxicity.
- 2.9 The PSCR (p1) agreed that the phrase “with/without surgical biopsy” can be removed from the proposed clinical criterion referring to HRCT. The PSCR also agreed with the clarifications made to the FVC criterion but requested that “weight” be changed to “height”. The ESC agreed with the PSCR that “height” was more appropriate.
- 2.10 The ESC noted that if the PBAC recommended the listing of both nintedanib and pirfenidone, the restriction criteria would need to be made consistent; some additional changes in this regard were made to the above version of the requested restriction. In November 2015, the PBAC noted its concern that should both drugs become PBS subsidised in the future, the risk of concomitant use would need to be addressed (November 2015 pirfenidone PSD, paragraph 7.6). The Secretariat suggested including a criterion that nintedanib should not be used in combination with PBS-subsidised pirfenidone and noted that switching rules between the drugs may also need to be considered.

For more detail on PBAC’s view, see section 7 “PBAC outcome”.

3 Background

- 3.1 **TGA Status at time of PBAC consideration:** Pirfenidone was registered on the ARTG on 29 February 2016 for the treatment of IPF.
- 3.2 The PBAC previously considered a major submission for pirfenidone in November 2015 and a minor resubmission in March 2016. Table 1 provides a detailed summary of the March 2016 minor resubmission, relevant PBAC comments and changes in the current resubmission.
- 3.3 The PBAC also previously considered (but did not recommend) submissions for nintedanib for the treatment of patients with IPF at the March and November 2015 meetings.

Table 1: Summary of the previous submission and current resubmission

Component	March 2016 minor resubmission	Current resubmission
Requested PBS listing	Idiopathic pulmonary fibrosis, where the patient must have confirmed diagnosis of IPF as assessed by a multidisciplinary team, a predicted Forced vital capacity (FVC) $\geq 50\%$, and a predicted carbon monoxide diffusing capacity (DLCO) $\geq 30\%$. PBAC Comment: The PBAC noted that the minor resubmission did not explore the number of patients who may discontinue treatment based on the clinical trial evidence and the proposed model, stating that progression with treatment does not constitute treatment failure. The minor resubmission argued that, following a FVC decline $\geq 10\%$ with pirfenidone, continued treatment significantly reduced the risk of death and increased disease stabilisation compared to placebo patients who continued treatment with placebo following a FVC decline $\geq 10\%$. Noting this, the PBAC considered that implementing a stopping rule would be difficult in clinical practice. (paragraph 5.2, March 2016, PBAC PSD)	Same as previous submission
Requested price	Ex-manufacturer price: \$ [REDACTED] Effective ex-manufacturer price: \$ [REDACTED] Weighted DPMQ/pack: \$ [REDACTED]	Ex-manufacturer price: \$ [REDACTED] Effective ex-manufacturer price: \$ [REDACTED] Weighted DPMQ/pack: \$ [REDACTED]
Main comparator	Best supportive care	Same as previous submission
Clinical evidence	3 trials: ASCEND (n=555), CAPACITY-2 (n=435) and CAPACITY-1 (n=344) The resubmission presented additional supportive data from Nathan 2015. The submission claimed this evidence supported the assertion that patients continue to benefit from pirfenidone treatment following an FVC decline $\geq 10\%$.	Same as previous submission

Public Summary Document – November 2016 PBAC Meeting

Component	March 2016 minor resubmission	Current resubmission
Key effectiveness data	Unchanged from November 2015 submission.	Same as previous submission
Key safety data	Unchanged from November 2015 submission. The incidence of photosensitivity reaction, rash, stomach discomfort, dyspepsia, dysgeusia, nausea, anorexia, decreased appetite, weight decrease, asthenia, insomnia, dizziness, gastro-oesophageal reflux disease, fatigue and diarrhoea were significant higher in pirfenidone treated patients. Incidence of IPF and peripheral oedema was significantly lower in the pirfenidone treatment group when compared to placebo.	Same as previous submission
Clinical claim	Although not explicitly stated, it appears to be unchanged from November 2015 submission: superior efficacy and acceptable safety profile compared with placebo.	Same as previous submission
Economic evaluation	<p>Cost-utility model with cost/QALY \$45,000/QALY - \$75,000/QALY (10 year time horizon); \$45,000/QALY - \$75,000/QALY (16 year time horizon).</p> <p>The minor resubmission respecified the base case ICER through the following:</p> <ul style="list-style-type: none"> • removing the assumed price reduction following expiry of data exclusivity; • increasing the proposed rebate from █% to █%; and • providing the option of a 10 year or 16 year time horizon (the previous model only included the 16 year time horizon). <p>PBAC Comment: The PBAC recalled its concern from November 2015 that the use of historical data to extrapolate OS in the modelled BSC arm may have underestimated survival compared with the BSC arm in the trials. The PBAC noted the minor resubmission presented Kaplan-Meier curves comparing the survival in two IPF registries with the historical data. The PBAC considered that the survival demonstrated in the historical data was acceptably similar to that of the registries. (paragraph 5.4, March 2016 PBAC PSD)</p>	<p>Cost-utility model with cost/QALY \$45,000/QALY - \$75,000/QALY (10 year time horizon);</p> <p>Corrected error in removal of price reduction following expiry of data exclusivity</p>

Public Summary Document – November 2016 PBAC Meeting

Component	March 2016 minor resubmission	Current resubmission
Number of patients	Unchanged from November 2015 submission. Less than 10,000 in Year 1 increasing to less than 10,000 in Year 5. PBAC Comment: The PBAC recalled its key concerns in November 2015 regarding the derivation of the pirfenidone treated population (potentially higher IPF incidence rate; limiting calculation of prevalent population to IPF patients in the year prior to listing) and hospitalisations are likely to result in underestimated net costs to the government. The evaluation also noted additional factors (application of ABS population projections; potential duplication of deaths in the pirfenidone treatment continuation rates) that were likely to further contribute to this underestimate. The PBAC considered that the minor resubmission did not sufficiently address these issues, and noted the potential for the absence of a stopping rule to increase the utilisation estimates. (paragraph 5.7, March 2016, PSD).	Calculation of patients treated changed from number of patients treated per year to Patient-years of treatment, based on quarters of treatment. Less than 10,000 in Year 1 to less than 10,000 in Year 5.
Estimated cost to PBS	\$30 - \$60 million in Year 1 increasing to \$60 - \$100 million in Year 5.	\$30 - \$60 million in Year 1, increasing to \$60 - \$100 million in Year 5 for a total of more than \$100 million over the first 5 years of listing RSA subsidisation caps proposed of \$ [REDACTED] million over the first 5 years of listing.
PBAC decision	Reject PBAC Comment: The PBAC did not recommend the PBS listing of pirfenidone for the treatment of idiopathic pulmonary fibrosis on the basis of unacceptably high cost effectiveness, in the context of total cost and uncertain utilisation. (paragraph 5.1, March 2016 PBACPSD)	-

For more detail on PBAC's view, see section 7 "PBAC outcome".

4 Clinical place for the proposed therapy

- 4.1 IPF is a specific form of chronic, progressive, fibrosing, idiopathic interstitial pneumonia (IIP). It is the most common IIP and the most severe and frequently occurring of the broader category of all interstitial lung diseases (ILD). IPF is an irreversible and fatal disease with considerable variability in disease progression and median survival ranging from 3 to 5 years. IPF causes a progressive decline in lung function, which increasingly restricts routine physical activity due to breathlessness from disrupted alveolar-capillary barrier architecture, leading to impaired gas exchange and increased work of breathing due to reduced compliance of the lungs. Lung transplant is the only potentially curative intervention for IPF.
- 4.2 No other medications are currently listed on the PBS specifically for the treatment of IPF. A resubmission for nintedanib for the treatment of IPF was also considered by the PBAC at the November 2016 meeting (agenda item 4.02 refers).

- 4.3 The ESC noted that the complete mechanism of action of pirfenidone is yet to be fully established; however, existing data indicates anti-fibrotic, anti-inflammatory and anti-oxidant properties in a variety of in vitro systems and animal models of pulmonary fibrosis. By comparison, nintedanib is a small molecule tyrosine kinase inhibitor which blocks intracellular signalling associated with the proliferation, migration and transformation of fibroblasts, which are mechanisms of IPF pathology.
- 4.4 As in the November 2015 and March 2016 submissions, the current resubmission proposed that pirfenidone be used in combination with BSC for the treatment of IPF.

For more detail on PBAC's view, see section 7 "PBAC outcome".

5 Comparator

- 5.1 As in the November 2015 and March 2016 submissions, the current resubmission nominated BSC as the main comparator. Nintedanib was also included as a secondary comparator. In November 2015, the PBAC reaffirmed that BSC was the appropriate main comparator for pirfenidone for IPF, and noted that nintedanib was also a relevant comparator (November 2015 pirfenidone PSD, paragraph 7.6).

For more detail on PBAC's view, see section 7 "PBAC outcome".

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The sponsor made arguments in support of the submission including the high clinical need for a PBS-subsidised drug for the treatment of IPF, the impact of the disease on quality of life and survival, and the impact of the drug on outcomes such as improved overall survival benefit. The sponsor reiterated its proposed RSA and provided clarification regarding ESC's comments on the extrapolation of overall survival in the model.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (50), health care professionals (5) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with pirfenidone including the ability to slow disease progression and improve quality of life. The comments also described the unmet need for an effective and PBS-subsidised treatment for IPF, the financial burden associated with purchasing non-PBS subsidised pirfenidone and the risk of patients acquiring cheaper versions of pirfenidone online for which the safety and efficacy are uncertain.
- 6.3 The PBAC noted the advice received from the Lung Foundation Australia and the Australian Pulmonary Fibrosis Consortium that treatment with pirfenidone may slow disease progression and improve quality of life. The PBAC specifically noted the advice that the only access to relatively affordable medication for IPF (i.e. nintedanib or pirfenidone) is through importation. The advice noted that alternative treatment

Public Summary Document – November 2016 PBAC Meeting

consists of non-pharmacological interventions, such as pulmonary rehabilitation and oxygen therapy and, in a small proportion of patients, lung transplantation. The PBAC noted that this advice was supportive of the evidence provided in the submission.

Clinical trials

- 6.4 As in the March 2016 resubmission, the current resubmission was based on three head-to-head trials comparing pirfenidone with placebo: ASCEND (n=555), CAPACITY-2 (n=435) and CAPACITY-1 (n=344). A pooled meta-analysis of these trials was conducted, as was an indirect comparison comparing pirfenidone and nintedanib.
- 6.5 Details of the trials presented in the resubmission are provided in Table 2.

Public Summary Document – November 2016 PBAC Meeting

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Pirfenidone trials		
PIPF-016 (ASCEND)	Final Clinical Study Report – PIPF-016. A randomised, double-blind, placebo-controlled, phase 3 study of the efficacy and safety of pirfenidone in patients with idiopathic pulmonary fibrosis. King Jr TE, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis.	22 May 2014 The New England Journal of Medicine. 2014; 370 (22): 2083-2092
PIPF-004 (CAPACITY-2); PIPF-006 (CAPACITY-1)	Clinical Study Report – PIPF-004. A randomised, double-blind, placebo-controlled, phase 3, three-arm study of the safety and efficacy of pirfenidone in patients with idiopathic pulmonary fibrosis. Clinical Study Report – PIPF-006. A randomised, double-blind, placebo-controlled, phase 3 study of the safety and efficacy of pirfenidone in patients with idiopathic pulmonary fibrosis. Noble PW, Albera C, Bradford WZ, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): Two randomised trials. Albera C, Du Bois RM, Bradford WZ, et al. Prognostic significance of Surgical Lung Biopsy (SLB) in a well-characterized cohort of patients with Idiopathic Pulmonary Fibrosis (IPF). Sahn SA, Albera C, Du Bois RM, et al. Clinical outcomes with pirfenidone therapy in Treatment-adherent (TA) patients with Idiopathic Pulmonary Fibrosis (IPF). Valeyre D, Albera C, Du Bois RM, et al. 6 Minute Walk Distance (6MWD) And Forced Vital Capacity (FVC) In patients with Idiopathic Pulmonary Fibrosis (IPF): Similar pattern of pirfenidone response. Sahn SA, Albera C, Du Bois RM, et al. The effect of treatment with pirfenidone on progression-free survival in patients with Idiopathic Pulmonary Fibrosis (IPF): Exploratory analysis of outcomes using novel criteria for disease progression.	June 2009 June 2009 The Lancet. 2011; 377(9779): 1760-1769 American Journal of Respiratory and Critical Care Medicine. 2010; 181(1) American Journal of Respiratory and Critical Care Medicine. 2010; 181(1) American Journal of Respiratory and Critical Care Medicine. 2010; 181(1) American Journal of Respiratory and Critical Care Medicine. 2011; 183(1)
SP3	Taniguchi H, Ebina M, Kondoh Y, et al. Pirfenidone in idiopathic pulmonary fibrosis.	European Respiratory Journal. 2010; 35(4): 821-829
SP2	Azuma A, Nukiwa T, Tsuboi E, et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis.	American Journal of Respiratory and Critical Care Medicine. 2015; 171(9): 1040-1047

Source: Table B.2.3, p5-6 of Section B-DRT of the current resubmission

6.6 The key features of the direct randomised trials are summarised in Table 3.

Table 3: Key features of the included evidence

Trial ID	n	Treatment arms	Trial duration	Trial design	Primary outcome	Use in the economic evaluation
ASCEND	555	Pirfenidone 2403mg [^] /d: n=278 Placebo: n=277	52 weeks	R, DB, MC, MN, phase III	Change in FVC%Pred: baseline to week 52 (ASCEND) or week 72 (CAPACITY)	Kaplan-Meier estimates: overall survival (6.2 years follow-up*); progression free survival (log-normal parametric extrapolation), treatment duration (gompertz extrapolation); probability and duration of hospitalisations (CAPACITY 1 and 2)
CAPACITY-2	435	Pirfenidone 2403mg [^] /d: n=174 Pirfenidone 1197mg [^] /d: n=87 Placebo: n=174	72 weeks			
CAPACITY-1	344	Pirfenidone 2403mg [^] /d: n=171 Placebo: n=173				

[^] Maximum dose after completed 14-day titration

* Follow-up data from RECAP (long term extension study) also included in Kaplan-Meier estimates of survival and time to off treatment for pirfenidone; survival data for BSC was only available to 2 years.

Abbreviations: DB = double blind; FVC%Pred = forced vital capacity percent predicted; MC = multicentre; MN = multinational; R = randomised Source: Table B.2.5, p9-11, Section B-DRT of the current resubmission

Comparative effectiveness

6.7 Direct comparison with placebo: The key results from the trials and pooled meta-analyses are presented in Table 4; these have not changed since the November 2015 submission.

Table 4: Summary of results for key efficacy outcomes from the pirfenidone trials

Outcome		Pirfenidone vs placebo [^]		
		Individual trial results		Meta-analyses
Absolute change in FVC%Pred; MD (95% CI)	To week 72	CAPACITY-1	(- ,)	(- ,)
		CAPACITY-2	(,)	
	To week 52	CAPACITY-1	(- ,)	(,)
		CAPACITY-2	(,)	
		ASCEND	(,)	
FVC%Pred response - decline of ≥10% to 0%; RR (95% CI)	To week 52	CAPACITY-1	(,)	(,)
		CAPACITY-2	(,)	
		ASCEND	(,)	
Overall survival; HR (95% CI)	Cut-off: 52 weeks	CAPACITY-1	(,)	0.52 (0.31, 0.87)
		CAPACITY-2	(,)	
		ASCEND	0.55 (0.26, 1.15)	
	Vital status: end of study*	CAPACITY-1	1.07 (0.55, 2.08)	0.75 (0.50, 1.11)
		CAPACITY-2	0.65 (0.33, 1.29)	
		ASCEND	0.57 (0.28, 1.16)	
Progression free survival; HR (95% CI)	Cut off: 72 weeks	CAPACITY-1	0.84 (0.58, 1.22)	0.74 (0.57, 0.96)
		CAPACITY-2	0.64 (0.44, 0.95)	
	Cut off: 52 weeks	CAPACITY-1	0.78 (0.52, 1.15)	0.62 (0.51, 0.75)
		CAPACITY-2	0.58 (0.50, 0.83)	
		ASCEND	0.57 (0.43, 0.77)	
		ASCEND	0.57 (0.43, 0.77)	
Time to worsening of IPF; HR (95% CI)	Cut off: 72 weeks	CAPACITY-1	0.73 (0.43, 1.24)	0.78 (0.54, 1.14)
		CAPACITY-2	0.84 (0.50, 1.42)	

Abbreviations: FVC%Pred=forced vital capacity percent predicted; IPF=idiopathic pulmonary fibrosis; HR=hazard ratio; MD=mean difference; 95% CI=95% confidence interval; RR=relative risk

Figures in **bold** indicate results that are statistically significant.

* Vital status – end of study: deaths that occurred at any time during the study regardless of whether patients continued on study treatment or study assessments

[^] The results of the meta-analyses presented in the submission omitted numerous variables recommended by the PBAC Guidelines (version 4.4, pp104-105): statistical measures of relative risk (RR) and accompanying 95% confidence intervals for relative difference (RD) and mean difference (MD). Meta-analyses analyses in italics, with the exception of overall survival (vital status: end of study), were conducted during the evaluation using StatsDirect version 2.7.9 using the DerSimonian-Laird random effects model.

Source: Table B.6.1, 7.09.COM.28.

- 6.8 Indirect comparison with nintedanib: A brief summary of results from the indirect comparison with nintedanib is provided in Table 5. The redacted table below shows no statistically significant difference in change from baseline to Month 12 in percent predicted FVC between pirfenidone compared with nintedanib.

Table 5: Summary of results from the indirect comparison of pirfenidone and nintedanib

Outcome		Indirect comparison: pirfenidone vs nintedanib
Change in FVC%Pred	Mean difference (95% CI)	(- ,)
All-cause mortality	HR (95% CI)	(,)
IPF-related mortality	HR (95% CI)	(,)

Abbreviations: CI=confidence interval; FVC = forced vital capacity; HR=hazard ratio.

Source: Table B(i).6.2, B(i).6.4- B(i).6.5, p27, 29-30 of Section B-ICRT of the current resubmission

- 6.9 In November 2015, the PBAC considered that interpretation of the indirect comparison with nintedanib was difficult given the differences in the trial populations and the outcomes. A network meta-analysis published by Loveman et al 2015 provided conflicting data which suggested a trend to better overall survival for pirfenidone (OR = 1.39, 95% CI: 0.70, 2.82), but a superior benefit in slowing FVC decline for nintedanib (OR = 0.67, 95% CI: 0.51, 0.88) and a trend to better

prevention of exacerbations with nintedanib (no OR provided but only nintedanib had a superior result to placebo). The PBAC considered both drugs are likely to be similarly clinically effective (November 2015 PSD, paragraph 7.11).

- 6.10 A Bayesian meta-analysis by Rochweg¹ (2016) compared treatments for IPF and graded the available evidence using GRADE criteria. The authors concluded that there was no significant difference between nintedanib and pirfenidone, and that the certainty of the evidence for this was moderate. These results were consistent with those of Loveman (2015).
- 6.11 Since the evaluation, an additional meta-analysis (Rogliani et al 2016²) was identified. The findings in this publication appeared to be consistent with the conclusions in Loveman 2015, suggesting a signal for greater effectiveness for nintedanib in slowing decline in FVC, compared with pirfenidone. The ESC noted the concluding statement in the paper that “the precautionary approach of...not strongly recommending specific medication for use in IPF is understandable. Further precaution should be taken in transposing the results obtained from different meta-analysis in every day clinical practice...methodological discrepancies across meta-analysis may led [sic] to different results.”

Comparative harms

- 6.12 Key results from the meta-analyses of safety outcomes are presented in Table 6.

¹ Rochweg B, Neupane B, Zhang Y, Garcia CC, Raghu G, Richeldi L, Brozek J, Beyene J, and Schünemann. Treatment of idiopathic pulmonary fibrosis: a network meta-analysis. *BMC Medicine*, 2016; 14: 18

² Rogliani P, Calzetta L, Cavalli F et al. Pirfenidone, nintedanib and N-acetylcysteine for the treatment of idiopathic pulmonary fibrosis: A systematic review and meta-analysis. *Pulmonary Pharmacology & Therapeutics* 40(2016): 95-103.

Table 6: Summary of the meta-analyses of key safety outcomes from the pirfenidone trials

Safety outcomes		Meta-analysis* (ASCEND, CAPACITY 1 and 2): RR (95% CI)	
Overall safety outcomes			
Number of patients with any TEAEs			
Any treatment related TEAEs			
Patients with AEs leading to discontinuation			
Patients with treatment emergent SAEs			
Common adverse events (>5%)			
Gastrointestinal disorders	Stomach discomfort		
	Dyspepsia		
	Nausea		
	GORD		
General disorders	Asthenia		
	Fatigue		
	Oedema peripheral		
Investigations	Weight decreased		
Metabolism and nutrition disorders	Anorexia		
	Decreased appetite		
Nervous system disorders	Dysgeusia		
	Dizziness		
Psychiatric disorders	Insomnia		
Respiratory disorders	IPF		
Skin & subcutaneous tissue disorders	Photosensitivity reaction		
	Rash		

Abbreviations: AE= adverse event; GORD = gastro-oesophageal reflux disease; IPF = idiopathic pulmonary fibrosis; SAE = serious adverse event; TEAE = treatment emergent adverse event; RR=relative risk; 95% CI=95% confidence interval

* The evaluation noted that it appeared that the submission used a fixed effects model in the meta-analyses of safety data. This is not consistent with the PBAC Guidelines (Version 4.4, p107), which recommend the random effects model when conducting a meta-analysis. The re-calculation of estimates was not feasible during the evaluation, due to the extensive number of adverse event items reported in the main body of the submission. Overall, it was unclear whether a random effects analysis would substantively impact on the interpretation of the safety results.

Source: Table B.6.9, p59 and Table B.6.10, p61-63, Section B-DRT of the submission of the current resubmission

- 6.13 In November 2015, the PBAC noted “pirfenidone was associated with statistically significantly higher instances of adverse events in several items across system organ classes. The highest relative differences were observed in the skin and subcutaneous tissue disorders (photosensitivity reaction, rash) and gastrointestinal disorders (stomach discomfort, dyspepsia). Also, a significant increase was observed in gastro-oesophageal reflux disease, a known co-morbidity of IPF. A statistically significant reduction in peripheral oedema was observed.” (November 2015 PSD, paragraph 7.10)
- 6.14 Common (>5%) adverse events associated with nintedanib include diarrhoea, nausea, vomiting and dyspnoea (nintedanib November 2015 PSD, Table 6). A statistically significant difference was also observed for arterial thromboembolic events (nintedanib November 2015 PSD, paragraph 6.17).

Benefits/harms

- 6.15 A summary of the comparative benefits and harms for pirfenidone versus placebo is presented in the following table.

Table 7: Summary of comparative benefits and harms for pirfenidone and placebo

Trial	Pirfenidone	Placebo	Absolute difference: median survival		HR% (95% CI)		
Benefits							
Overall survival: vital-status – end of study							
ASCEND, CAPACITY-1 & 2	44/623	58/624	NA		0.75 (0.50,1.11)		
Absolute change in FVC%Pred from baseline to week 52[^]							
	Pirfenidone			Placebo			Mean difference (95% CI): Pirfenidone vs. placebo
	n	Mean Δ baseline	SD	n	Mean Δ baseline	SD	
CAPACITY-1	171	-5.0	█	173	-6.9	█	█
CAPACITY-2	174	-4.4	█	174	-9.2	█	
ASCEND	278	-6.2	█	277	-	█	
Harms[^]							
	Pirfenidone	Placebo	RR (95% CI)	Event rate/100 patients*		RD% (95% CI)	
				Pirfenidone	Placebo		
Photosensitivity reaction							
ASCEND, CAPACITY-1 & 2	█	█	█	█	█	█	
Rash							
ASCEND, CAPACITY-1 & 2	█	█	█	█	█	█	
Stomach discomfort							
ASCEND, CAPACITY-1 & 2	█	█	█	█	█	█	

Abbreviations: RD = risk difference; RR = risk ratio; FVC%Pred = Forced vital capacity percent predicted

* Duration: ASCEND = 52 weeks; CAPACITY-2 = 72 weeks; CAPACITY-1 = 72 weeks

[^] Mean difference, relative risk and risk difference (%) were calculated from the meta-analysis of ASCEND, CAPACITY-1 and CAPACITY-2 according to the random effects model (DerSimonian-Laird; StatsDirect Version 2.7.9).

Source: Compiled during the evaluation

- 6.16 On the basis of direct evidence presented by the submission (for baseline to week 52), in comparison to placebo, pirfenidone was associated with:
- Approximately a 4.0% reduction in absolute change in FVC%Pred.
 - No significant difference for overall survival as reported in the vital status-end of study analysis (this analysis was considered in an FDA review for pirfenidone to be most representative of the efficacy of a drug in terms of disease modification/survival).
- 6.17 On the basis of direct evidence presented by the submission, for every 100 patients treated with pirfenidone in comparison to placebo, over 52-72 week duration of follow-up, approximately:
- 8 additional patients would have a photosensitivity reaction.
 - 20 additional patients would have a rash.
 - 6 additional patients would have stomach discomfort.

Clinical claim

- 6.18 As in the November 2015 and March 2016 submissions, the current resubmission described pirfenidone as having superior efficacy and an acceptable safety profile compared with placebo. In November 2015, the PBAC considered that pirfenidone is

superior in efficacy to placebo and has an inferior safety profile (November 2015 PSD, paragraph 6.26).

- 6.19 The current resubmission did not make an explicit clinical claim against nintedanib, but did state that the results of the indirect comparisons suggest that treatment with pirfenidone is non-inferior to nintedanib in FVC, all-cause mortality and IPF-related mortality, and that pirfenidone and nintedanib have a similar overall safety profile. In November 2015, the PBAC considered that “interpretation of the indirect comparison with nintedanib is difficult given the differences in the trial populations and the outcomes... However, PBAC considered both drugs are likely to be similarly clinically effective” (November 2015 PSD, paragraph 7.11).
- 6.20 The ESC considered that no new evidence was presented that would be sufficient to change the PBAC’s previous conclusion that nintedanib and pirfenidone are likely to be similarly clinically effective.
- 6.21 The PBAC reaffirmed that the claim of superior effectiveness and inferior safety, compared with placebo, was reasonable. The PBAC also reaffirmed that pirfenidone and nintedanib are likely to be similarly clinically effective.

Economic analysis

- 6.22 The current resubmission presented an updated economic model to evaluate the cost-effectiveness of pirfenidone versus BSC. The changes made since the March 2015 minor resubmission consisted of:
- Correcting an error in the previous model’s calculation of treatment costs. Specifically, when the price reduction following market entry was switched off, instead of reverting back to the ■% rebate offered on the ex-manufacturer price, the rebate was incorrectly removed altogether. Consequently after 5 years, the full price of pirfenidone was applied rather than taking into account the ■% rebate.
 - Unit costs were also updated to reflect current prices.
- No other substantive changes were made to the structure or rationale of the economic model (refer to Table 8, below).

Public Summary Document – November 2016 PBAC Meeting

Table 8: Summary of model structure and rationale

Time horizon	10 years in the model base case versus 72 weeks in the pirfenidone CAPACITY trials and 52 weeks in the ASCEND trial (plus an open-label extension study to 6.2 years)
Outcomes	LYG and QALYs
Methods used to generate results	Partitioned survival model
Health states	PFS, progression, lung transplant, death
Cycle length	0.25 years; half cycle correction applied
Transition probabilities	Overall survival <ul style="list-style-type: none"> • Pirfenidone patients: Weibull function fitted to pooled K-M data to 6.2 years, then Weibull function from Strand 2014 to 10 years • BSC patients: K-M data to 2 years, then K-M Strand 2014 data to 6.2 years, then Weibull function from Strand 2014 to 10 years. PFS <ul style="list-style-type: none"> • Pirfenidone patients: a lognormal function is fitted to K-M data pooled trial data from the median follow-up of 16 months to extend PFS to 10 years. • BSC patients: a lognormal function is fitted to K-M data pooled trial data to extend PFS to 10 years.
Discount rate	5% for costs and outcomes
Software package	Excel 2010.

Source: compiled during the evaluation.

- 6.23 In November 2015, the PBAC raised concerns regarding the applicability of historical data from a single source (Strand 2014) to inform the extrapolation of OS in the BSC arm (November 2015 PSD, paragraph 7.16). In March 2016, the PBAC considered that the survival demonstrated in the historical data (Strand 2014) was acceptably similar to data presented in the minor resubmission from two IPF patient registries (Invoa and Edinburgh) (March 2016 PSD, paragraph 5.4). The Inova IPF registry and the Edinburgh IPF registry data were unchanged in the current resubmission.
- 6.24 As in the March 2016 minor resubmission, the current resubmission stated that in order to achieve comparability of the real-world data from these registries and the clinical data available for pirfenidone, “propensity score models were used to match the registry cohorts to patients treated with BSC that could have been enrolled in the pivotal trials for pirfenidone, based on the inclusion/exclusion criteria.” (p16, Section C of current resubmission). The resubmission presented the output of the analysis and stated that “[the sponsor] now seeks a thorough evaluation of this validation approach as part of this major resubmission.” (p17, Section C of the current resubmission). A full evaluation of the validation approach was not possible because the submission only included the output of the analyses, and gave no details on how the data was propensity scored or matched.
- 6.25 The submission did not provide any justification for the selection of the registries. A targeted search conducted during the evaluation yielded a large, but not comprehensive, list of other IPF registries and observational cohorts: Australian Lung Foundation Idiopathic Pulmonary Fibrosis Registry, Pennsylvania Idiopathic Pulmonary Fibrosis State Registry (PAIPF), IPF PRO (USA), European MultiPartner IPF Registry (EMPIRE; Eastern and Central Europe, INSIGHTS IPF Registry (Germany), European IPF Registry and Biobank, Prospective Study of Fibrosis in the Lung Endpoints (PROFILE – Central England), British Thoracic Society Interstitial Lung Disease Registry Programme. Considering the number of other possibly viable registries to base these analyses on, and the fact that only two were selected with no

explanation or justification, the risk of selection bias was high. The current resubmission should have conducted its pre-modelling study using the approach previously used for the selection of the Strand 2014 study, including, a systematic search of IPF registries and discussion of the identified registries, and reasons for exclusion from the analysis. The evaluation acknowledged that many of the aforementioned registries would potentially be excluded from analysis due to lack of sufficient data. The PSCR (p3) confirmed that the reason for the selection of the Edinburgh and Inova registries was solely the accessibility of patient level data from cohorts that were large enough to allow further analysis. This allowed for the selection of patients from the registry cohorts based on matched characteristics with patients from the pivotal trials for pirfenidone.

- 6.26 The evaluation noted that propensity score matching (PSM) is typically used to estimate differences in treatment effect, rather than confirm similarity of outcomes. PSM is also typically conducted on two separate groups (i.e. treatment and placebo). It was therefore unclear what the rationale of the analysis was and how the analysis was performed. PSM is typically comprised of two parts³:
- i. The propensity scoring, where the probability of treatment assignment conditional to observed baseline covariates is ascertained usually through a logistic regression. The current resubmission stated that the matching occurred on the basis of the CAPACITY trial's inclusion criteria. The ESC noted that the resubmission did not specifically indicate which criteria were included as covariates in the propensity model and gave no details on model parameters. If only age, gender, FVC%Pred and DLco%Pred were included as covariates, the question must be raised as to whether these covariates were sufficient predictors of survival in IPF without other covariates such as smoking status, comorbidities, etc.
 - ii. The matching, where sets of treated and untreated subjects who share a similar value of the propensity score are formed. Typically, matched pairs are formed, with one treated subject and one untreated subject. The ESC noted that the current resubmission did not specify a matching rule and the data being matched were not made clear. It was unclear who the "patients treated with BSC that could have been enrolled in the pivotal trials" were and what the aim was of matching to registry cohorts.
- 6.27 The PSCR acknowledged that the covariates accounted for in the PSM analysis did not account for predictors of OS such as smoking status and comorbidities. Consequently, the validity of the analysis is limited by the completeness of the covariates included. Additionally, the ESC noted that it would have been informative to review Kaplan-Meier curves after applying the inclusion criteria, but before applying the propensity score trimming to assess the effect of the scoring on the estimated survival. Overall, the ESC considered that it was unclear how PSM was used and whether the methodology was appropriate.
- 6.28 Table 9 presents the key drivers of the model.

³ Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res.* 2011; 46(30).

Public Summary Document – November 2016 PBAC Meeting

Table 9: Key drivers of the model

Description	Method/Value	Impact
Survival extrapolation	Pirfenidone: Weibull function fitted to pooled K-M data to 6.2 years, Weibull function from Strand 2014 to 10 years BSC: K-M data to 2 years, then K-M Strand 2014 data to 6.2 years, Weibull function from Strand 2014 to 10 years	High, favoured pirfenidone
PBS Category/Program	Section 100 Highly Specialised Drugs	Moderate, favoured pirfenidone
Progression state utility	Progression state utility = 0.74	Moderate, favoured pirfenidone

Source: compiled during the evaluation

6.29 Table 10 presents the summarised results of the stepped economic evaluation.

Table 10: Results of the stepped economic evaluation

Step and component	Pirfenidone	BSC	Increment
Step 1: trial-based costs and outcomes (2 years)			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
LY	[REDACTED]	[REDACTED]	[REDACTED]
QALY	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
Step 2: modelled evaluation (extrapolation beyond clinical trials; 10 years)			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
LY	[REDACTED]	[REDACTED]	[REDACTED]
QALY	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
Steps 3: modelled evaluation (incorporation of medical MRU costs; AE related costs, lung transplant costs and outcomes and end of life costs; 10 years)			
Costs	\$ [REDACTED]	\$38,649	\$ [REDACTED]
LY	[REDACTED]	[REDACTED]	[REDACTED]
QALY	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
Step 4: modelled evaluation (incorporation of proposed rebate; 10 years)			
Costs	\$ [REDACTED]	\$38,649	\$ [REDACTED]
LY	[REDACTED]	[REDACTED]	[REDACTED]
QALY	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]

Source: Tables D.5.1 to D.5.7, pp21 – 26 of the current resubmission

Abbreviations: BSC = best supportive care, LY = life years, QALY = quality adjusted life years.

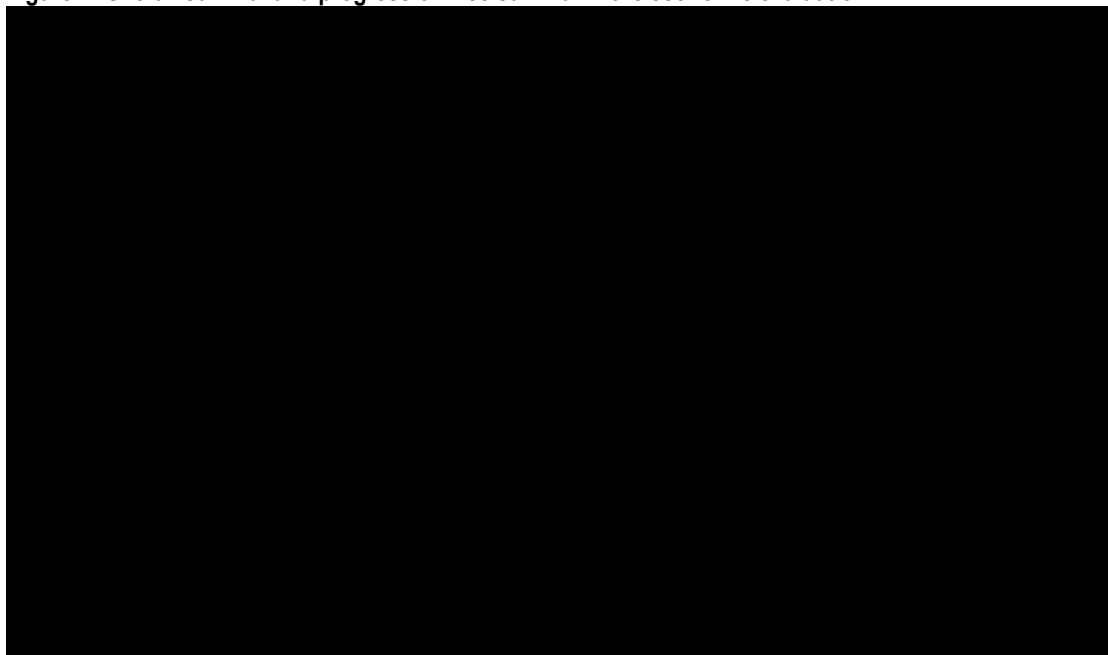
6.30 Correcting the error noted above regarding the application of the rebate in the March 2016 model reduced the March 2016 base case ICER (using a 10 year horizon) from \$45,000 - \$75,000 per QALY to \$45,000 - \$75,000per QALY. In comparison, the base case of the current resubmission was \$45,000 - \$75,000per QALY. The correction of the model was the only change in the current resubmission with a significant impact on the ICER.

6.31 Considering pirfenidone need not be administered in a hospital setting, the ESC considered that it was reasonable to consider the cost-effectiveness of a General Schedule listing for pirfenidone. Listing pirfenidone under the General Schedule (resulting in additional mark-ups, which would increase the DPMQ by \$ [REDACTED])

compared with the public hospital S100 HSD DPMQ) would increase the ICER from \$45,000 - \$75,000 per QALY to \$45,000 - \$75,000 per QALY.

- 6.32 In November 2015, the PBAC had considered that “utility values sourced from the literature appeared reasonable, however, given the age of the proposed eligible PBS population they may overstate the utility associated with progression.” (November 2015 PSD, paragraph 7.17). The model continued to be sensitive to the progression state utility value. For example, a 10% decrement on the progression utility value increased the ICER to \$45,000 - \$75,000 per QALY.
- 6.33 The ESC noted that a large proportion (95%) of the estimated survival gain is from the extrapolated part of the survival curves (specifically from the period beyond which randomised trial data are available). The pre-PBAC response (p2) noted the following data were used to generate the survival gain:
- Years 0-2: data from the randomised controlled portions of the CAPACITY and ASCEND trials;
 - Years 2-6.2: data from the RECAP long-term extension study for pirfenidone and the Stand 2014 registry for BSC; and
 - Years 6.2-10: a Weibull function was fitted to the Strand registry data and the resulting death rates were used for both pirfenidone and BSC.
- The pre-PBAC response further noted that only a third (36%) of the estimated overall survival gain was from the period between 6.2 years and 10 years, and that two thirds was informed by the best available long-term data for both pirfenidone and BSC.
- 6.34 The ESC noted the larger incremental survival benefit modelled, compared with progression free survival (as represented by the respective areas between the pirfenidone and BSC curves in Figure 1) and expressed concern that the modelled survival appeared unrealistic. The ESC considered this may be due to a healthy cohort bias due to the use of registry data in informing the extrapolations of survival in the pirfenidone model. The pre-PBAC response (p2) stated that the larger incremental survival benefit modelled “is explained by the disease characteristics of IPF and the fact that, unlike oncology, progression does not indicate treatment failure. ... The submission does not claim that PFS is a surrogate for OS or that treatment effect is dependent of PFS. It is therefore not implausible that more incremental survival is gained in progressive disease than in PFS. Advisory Board feedback of 7 clinicians confirmed that the modelled survival curves are an appropriate representation of PFS and OS associated with pirfenidone + BSC and BSC alone in patients with mild to moderate IPF in Australian clinical practice.”

Figure 1: Overall survival and progression free survival in the economic evaluation



Source: "Updated Economic Evaluation Major Resubmission.xlsx" OS = overall survival; PFS = progression free survival

- 6.35 The PBAC noted that while the modelled time horizon was truncated to 10 years, the differences in extrapolated PFS and OS did not converge until 20 years. The PBAC considered that this approach may have overestimated the incremental benefit in OS associated with treatment with pirfenidone compared with BSC.
- 6.36 The ESC noted the challenges of making comparisons across the nintedanib and pirfenidone submissions for IPF given that the two submissions adopted distinct modelling approaches.

Drug cost/patient/year: \$ [REDACTED]

- 6.37 As in the March 2016 resubmission, the current resubmission estimated patients would receive [REDACTED] scripts per year. Using the weighted DPMQ of \$ [REDACTED], the drug cost per patient per year was estimated to be \$ [REDACTED].

Estimated PBS usage & financial implications

- 6.38 This resubmission was considered by DUSC. The current resubmission followed the same general approach to estimating use as the previous submissions, with the following change: instead of patients treated per year, the resubmission calculated pirfenidone treatment quarters and divided the number of treatment quarters by four to estimate the number of patient treatment years in each year of listing. DUSC considered that the approach to the financial estimates was complex and not fully transparent, as the independent contribution of deaths and discontinuations to the retention rate could not be determined. While DUSC identified some issues in the derivation of the patient estimates in relation to the application of treatment discontinuations, DUSC noted that the patient treatment years in the resubmission did not greatly differ from the estimated number of patients treated in the March 2016 submission.

6.39 Table 11 presents the estimated use and financial implications. The redacted table below shows that at year 5 the estimated number of patients was less than 10,000 per year and annual subsidisation caps limiting PBS expenditure to \$ [REDACTED] million over the five years.

Table 11: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Incident IPF population	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Eligible incident population	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Patient treatment years	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total number of treated patients	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Patients treated with pirfenidone (March 2016)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Pirfenidone packs dispensed by PBS/RPBS (10.66 packs per patient per year)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Pirfenidone packs (March 2016)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Net costs to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
March 2016 resubmission	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Proposed subsidisation caps for PBS expenditure	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net costs to MBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
March 2016 resubmission	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net savings to state and territory governments	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
March 2016 resubmission	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Overall net cost to government	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
March 2016 resubmission	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Compiled during the evaluation

6.40 DUSC considered the number of eligible patients in the submission may have been underestimated. However, DUSC considered the number of treated patients in the later years may have been overestimated. Despite methodological issues, overall the number of full patient years on treatment may be a reasonable estimate. The main issues were:

- The estimated number of incident patients relied on a narrow definition of IPF, thus the eligible proportion of 66% may have been underestimated.
- The estimated number of patients treated relied on application of the same retention rate to the prevalent pool as for incident patients, which may have overestimated the number of continuing patients.

6.41 DUSC noted that the November 2016 resubmission for nintedanib adopted a different approach to estimating use in practice compared with the pirfenidone resubmission. DUSC made the following general points regarding the financial estimates for IPF therapies to assist the PBAC in aligning these different approaches:

- DUSC recalled its view that the population prevalence of IPF based on studies consistent with the restriction is 14.4 per 100,000 (Nintedanib IPF PSD March 2015). If this population prevalence is applied to the projected Australian population, the diagnosed prevalent patient pool would be between 3,300 and 3,600 over the five year estimates.

- Because the prevalence rate includes diagnosis, DUSC considered that close to 100% of the prevalent pool would meet the restriction eligibility criteria.
- DUSC recalled its view that, given that IPF is a progressive and ultimately fatal disease with no other specific therapies available in Australia, uptake in the eligible population would be substantial (nintedanib (IPF) PSD March 2015). DUSC recommended uptake rates of 60% in year 1 increasing to 100% in year 5.
- DUSC considered that tolerability in practice might be lower than in the clinical trials, meaning patients may not persist with therapy to the same extent.

6.42 The pre-PBAC response noted that DUSC considered that the prevalent population eligible for treatment is between 3,300 and 3,600 patients which represents 66% to 72% of the 5,000 prevalent patients with IPF estimated by the Lung Foundation Australia. Therefore, the pre-PBAC response concluded that the 66% eligibility rate is within a range deemed reasonable by DUSC.

Quality Use of Medicines

6.43 The dosing regimen for pirfenidone is three capsules three times per day. DUSC considered the dosing regimen may have implications for patient compliance, particularly in the context of a treatment that does not result in improvement of symptoms.

Financial Management – Risk Sharing Arrangements

- 6.44 The resubmission proposed an RSA consisting of two parts:
- An SPA with a ■■■% rebate on the ex-manufacturer price (as proposed in the March 2016 minor resubmission); and
 - Annual subsidisation caps with ■■■% rebate of PBS expenditure exceeding the caps; limiting PBS expenditure to \$■■■■ million over five years.
- 6.45 DUSC considered there would be potential for use of pirfenidone outside the requested restriction in other subtypes of interstitial lung disease, which also have limited treatment options. While this risk would likely be mitigated by the suggested authority listing and the requirement for diagnosis by a multidisciplinary team, DUSC considered a tight RSA was important.
- 6.46 The resubmission stated that due to the proposed tight subsidisation caps, the presented results of the financial estimates are of limited relevance for PBAC's decision making. While DUSC acknowledged the subsidisation caps proposed by the sponsor were provided to mitigate against high total cost to government, DUSC disagreed with the sponsor that the financial estimates are of limited relevance. DUSC considered estimating the extent of use is important for future monitoring and ensuring quality use of medicines. DUSC also noted that the sponsor did not provide any reasoning for the cap amounts in each of the five years.

For more detail on PBAC's view, see section 7 "PBAC outcome".

7 PBAC Outcome

- 7.1 The PBAC deferred making a recommendation on whether pirfenidone should be listed for the treatment of idiopathic pulmonary fibrosis (IPF) to allow for further discussions regarding an acceptable price and RSA.
- 7.2 The PBAC recalled that in March 2016, the PBAC did not recommend listing pirfenidone for the treatment of IPF on the basis of unacceptably high cost-effectiveness, in the context of the total cost and uncertain utilisation.
- 7.3 As per its previous considerations in November 2015 and March 2016, the PBAC recognised the high clinical need for an effective treatment for IPF and the significant debilitating effects of the disease on quality of life, as noted in the consumer comments received for this item. The PBAC noted that the American Thoracic Society guidelines for the treatment of IPF (2015 update⁴) conditionally recommend the use of pirfenidone and nintedanib for the treatment of IPF (with moderate confidence in the effect estimates for both drugs).
- 7.4 The PBAC noted that IPF is a heterogeneous disease with different clinical courses but ultimately a poor prognosis. In noting the difficulty of diagnosis of IPF and the comments from the Australian IPF registry steering committee, the PBAC recommended that a PBS restriction for pirfenidone should include a criterion requiring diagnosis by a multidisciplinary team, defined as a respiratory physician, radiologist and, where histological material is considered, a pathologist. The PBAC also recommended the following with regards to the requested listing:
- Given that administration of pirfenidone within a hospital setting is not required, listing on the General Schedule listing would be more appropriate.
 - That a PBS listing for pirfenidone should not include a continuation rule as it would be difficult to implement in practice. The PBAC noted that in progressive conditions like IPF, deterioration in lung function is not inconsistent with a treatment benefit and that no continuation rule was implemented in the clinical trials. The risk of continued use in patients who have progressed and are therefore likely to receive a relatively smaller benefit of treatment should be managed through an RSA.
 - Retain the requirement for a chest HRCT scan to be consistent with diagnosis of IPF.
 - Removal of the population criterion restricting use to patients aged 40 years and over.
- 7.5 The PBAC reaffirmed that best supportive care was an appropriate comparator for pirfenidone for IPF. Another novel agent for the treatment of IPF, nintedanib, was also considered at the November 2016 PBAC meeting and was a relevant secondary comparator.
- 7.6 The PBAC noted the resubmission presented the same three head-to-head randomised clinical trials comparing pirfenidone with placebo as in the March 2016 and November 2015 submissions: ASCEND (n=555), CAPACITY-2 (n=435) and

⁴ An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline. Raghu et al. April 2015. <https://www.thoracic.org/statements/resources/interstitial-lung-disease/IPF-Full-length.pdf>.

CAPACITY-1 (n=344). A pooled meta-analysis of these trials was conducted, as was an indirect comparison comparing pirfenidone and nintedanib. On the basis of direct evidence in comparison to placebo presented by the submission, pirfenidone was associated with:

- Approximately a 4.0% reduction in absolute change in FVC%Pred from baseline to week 52.
- No significant difference for overall survival, as reported in the vital status-end of study analysis (this analysis was considered in an FDA review for pirfenidone to be most representative of the efficacy of a drug in terms of disease modification/survival). The PBAC noted that the trials were not powered for survival and the duration of the trials was likely insufficient to detect an OS benefit.

- 7.7 The PBAC recalled that in November 2015 it considered an FDA⁵ review of pirfenidone and nintedanib studies suggested that FVC is a valid surrogate for mortality in IPF. It was further noted that the poor prognosis of patients with IPF combined with the observed trend in survival benefit imposes ethical limitations on any further placebo-controlled trials given the nature of the disease. This makes it difficult to generate prospective and placebo-controlled evidence of a statistically significant OS benefit with pirfenidone. Overall, PBAC considered that there may be indirect grounds to conclude that pirfenidone would likely improve OS, compared with BSC.
- 7.8 The PBAC noted that no new comparative safety evidence was presented in the current resubmission. The PBAC previously noted that common adverse events associated with pirfenidone include photosensitivity reaction, rash and gastrointestinal disorders.
- 7.9 The PBAC recalled that it previously considered pirfenidone and nintedanib to be similarly clinically effective (see paragraph 6.9). No new evidence was presented to change the PBAC's previous consideration.
- 7.10 The PBAC noted the challenges of making comparisons across the nintedanib and pirfenidone submissions for IPF given that the two submissions adopted distinct economic modelling approaches. The PBAC reiterated that the available comparative evidence suggested that the two drugs are likely to be similarly clinically effective. Accordingly, the PBAC considered that any difference in incremental life years gained between the pirfenidone and nintedanib models contradicted the clinical evidence and was an artefact of the different modelling approaches. The PBAC considered that the only inputs that should result in a difference in the cost effectiveness of pirfenidone and nintedanib are the proposed drug costs and, potentially, any differences in costs or quality of life associated with differences in comparative safety.
- 7.11 In its comparative assessment of the outcomes of the pirfenidone and nintedanib models, the PBAC considered that the pirfenidone model may have resulted in an overestimate of the incremental benefit (of 1.254 life years) and thus an underestimate of the ICER per QALY. In this regard, the PBAC considered that the ICER per QALY for pirfenidone may be significantly higher than \$45,000 -

⁵ Karimi-Shah BA, Chowdhury BA. Forced vital capacity in idiopathic pulmonary fibrosis-FDA review of pirfenidone and nintedanib. *The New England Journal of Medicine*. 2015;372(13):1189-91.

\$75,000per QALY (the base case ICER adjusted for listing on the General Schedule). Accordingly, the PBAC considered that the ICER per QALY was likely to be unacceptably high and uncertain at the requested price.

- 7.12 The PBAC agreed with the DUSC that there would be potential for use of pirfenidone outside the requested restriction in other subtypes of interstitial lung disease. While this risk would likely be mitigated by the authority required (in-writing) listing and the requirement for diagnosis by a multidisciplinary team, the PBAC considered that a tight subsidisation cap through an RSA would be important if recommended for listing. The PBAC further considered that all drugs listed on the PBS for the treatment of IPF should be included within a common financial cap. The PBAC noted that the sponsor did not provide any rationale for the cap amounts in each of the five years.
- 7.13 The PBAC noted that no basis was provided to assess the clinical effectiveness, safety and cost-effectiveness of combined use of pirfenidone and nintedanib for the treatment of IPF. Accordingly, the PBAC recommended that if both pirfenidone and nintedanib are PBS-subsidised in the future, a clinical criterion should be added to the pirfenidone restriction stating that “The treatment must not be in combination with PBS-subsidised nintedanib” (and vice versa for the nintedanib restriction). Any financial risk of concomitant use of PBS-subsidised pirfenidone and nintedanib despite this criterion would be managed through a common financial cap. The PBAC also noted that switching rules between the two drugs would be necessary.

Outcome:

Deferred

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor’s Comment

Roche is pleased that the PBAC recommended pirfenidone for PBS listing at its Special Meeting in December. Roche is awaiting further advice on the conditions of the recommendation from the Department of Health.

ADDENDUM

Subsequent to the November 2016 meeting, the sponsor provided the PBAC with the following information:

- a cost-minimisation analysis on the basis that the effective price for pirfenidone be no higher than the effective price for nintedanib at equi-effective doses;
- proposed equi-effective daily doses of 2,104.6 mg pirfenidone and 281.1 mg nintedanib;
- a comparison of prescribing, administration, safety and toxicity management profiles between pirfenidone and nintedanib;
- in principle agreement to join the risk sharing arrangement negotiated for nintedanib and to accept a common financial cap for both products.

NEW LISTINGS

At its meeting on **16 December 2016**, the PBAC decided to recommend to the Minister (under section 101(3) of the *National Health Act 1953* (“the Act”)) that pirfenidone be made available as a pharmaceutical benefit under Part VII of the Act, under certain circumstances (specified in accordance with section 101(3C) of the Act).

A note of the PBAC’s decision follows.

The PBAC recommended the listing of pirfenidone for the treatment of idiopathic pulmonary fibrosis (IPF) under certain conditions (see recommended listing) on a cost-minimisation basis to nintedanib.

The PBAC recalled that it previously considered nintedanib and pirfenidone to be similarly clinically effective and that it recommended nintedanib for IPF in November 2016 on a cost effectiveness basis. The PBAC considered that listing pirfenidone, such that the effective daily cost is no higher than that for nintedanib, would be appropriate. In this regard, the PBAC accepted the equi-effective daily doses proposed by the sponsor of 2,104.6 mg for pirfenidone and 281.1 mg for nintedanib, and considered that no other costs are relevant for inclusion in the calculation of the pirfenidone price.

The PBAC recommended the listing of pirfenidone should be consistent with the recommended restriction criteria for nintedanib with an additional clinical criterion stating that “The treatment must be the sole PBS-subsidised treatment for this condition”. The PBAC recommended that a similar note be added to the nintedanib restriction.

The PBAC recommended that an additional restriction, “Initial 2: change or re-commencement of treatment” should be included in the restrictions for both pirfenidone and nintedanib to allow for switching between the two drugs.

The PBAC recalled that nintedanib was recommended for IPF with a risk sharing arrangement which would cap Government financial expenditure based on the nintedanib submission’s financial estimates and a ■■■% rebate to any Government expenditure beyond the financial cap. The PBAC recommended that pirfenidone should be included within the same financial caps.

The PBAC advised that pirfenidone is not suitable for prescribing by nurse practitioners.

Public Summary Document – November 2016 PBAC Meeting

The PBAC advised, under Section 101(3BA) of the *National Health Act 1953*, that pirfenidone and nintedanib for the treatment of idiopathic pulmonary fibrosis should be treated as interchangeable on an individual patient basis.

The PBAC recommended that the Early Supply Rule should apply to pirfenidone.

Outcome:

Recommended

Recommended listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
PIRFENIDONE Capsules 267 mg, 270	1	5	Esbriet® Roche Products Pty Ltd

Category/Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Idiopathic pulmonary fibrosis
PBS Indication:	Idiopathic pulmonary fibrosis
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required - In Writing
Treatment phase:	Initial 1: new patient
Treatment criteria:	Must be treated by, or in consultation with, a respiratory physician or specialist physician.
Clinical criteria:	The condition must be diagnosed through a multidisciplinary team. AND Patient must have a chest high resolution computed tomography (HRCT) consistent with diagnosis of idiopathic pulmonary fibrosis within the previous 12 months AND Patient must have forced vital capacity (FVC) greater than or equal to 50% predicted for age, gender and height AND Patient must have a forced expiratory volume in 1 second (FEV1)/FVC ratio greater than 0.7 AND Patient must have diffusing capacity of the lungs for carbon monoxide (DLCO) corrected for haemoglobin equal to or greater than 30% AND Patient must not have interstitial lung disease due to other known causes including domestic and occupational environmental exposures, connective tissue disease, or drug toxicity. AND The treatment must be the sole PBS-subsidised treatment for this condition.
Prescriber Instructions	A multidisciplinary team is defined as comprising of at least a specialist respiratory physician, a radiologist and, where histological material is considered, a pathologist. If attendance is not possible, because of geographical isolation consultation with a multidisciplinary team is required for diagnosis. Application for authorisation for initial treatment must be in writing and must include: 1. A completed authority prescription form

Public Summary Document – November 2016 PBAC Meeting

	<p>2. A completed IPF Authority Application Supporting Information Form; and</p> <p>3. A signed patient acknowledgement.</p> <p>Patient must not have an acute respiratory infection at the time of FVC testing.</p>
Administrative Advice	<p>Special Pricing Arrangements apply.</p> <p>No increase in the maximum quantity will be authorised</p> <p>No applications for increased repeats will be authorised</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Prior Written Approval of Complex Drugs Reply Paid 9826 GPO Box 9826 HOBART TAS 7001</p>

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
PIRFENIDONE Capsules 267 mg, 270	1	5	Esbriet® Roche Products Pty Ltd

Category/Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Idiopathic pulmonary fibrosis
PBS Indication:	Idiopathic pulmonary fibrosis
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required - In Writing
Treatment phase:	Initial 2: change or re-commencement of treatment
Treatment criteria:	Must be treated by, or in consultation with, a respiratory physician or specialist physician.
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with nintedanib or pifenedone for this condition AND The treatment must be the sole PBS-subsidised treatment for this condition.
Prescriber Instructions	Application for authorisation for initial treatment must be in writing and must include: 1. A completed authority prescription form; and 2. A completed IPF Authority Application Supporting Information Form
Administrative Advice	<p>Special Pricing Arrangements apply.</p> <p>No increase in the maximum quantity will be authorised</p> <p>No applications for increased repeats will be authorised</p>

Public Summary Document – November 2016 PBAC Meeting

	<p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Prior Written Approval of Complex Drugs Reply Paid 9826 GPO Box 9826 HOBART TAS 7001</p>
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Category/Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Idiopathic pulmonary fibrosis
PBS Indication:	Idiopathic pulmonary fibrosis
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment phase:	Continuing treatment
Treatment criteria:	Must be treated by, or in consultation with, a respiratory physician or specialist physician.
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition. AND The treatment must be the sole PBS-subsidised treatment for this condition.
Administrative Advice	Special Pricing Arrangements apply. No increase in the maximum quantity will be authorised No applications for increased repeats will be authorised Authority applications for continuing treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Public Summary Document – November 2016 PBAC Meeting

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Category/Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Idiopathic pulmonary fibrosis
PBS Indication:	Idiopathic pulmonary fibrosis
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment phase:	Initial 3 - Grandfathering treatment
Treatment criteria:	Must be treated by, or in consultation with, a respiratory physician or specialist physician.
Clinical criteria:	<p>Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to [listing date].</p> <p>AND</p> <p>The condition must have been diagnosed through a multidisciplinary team.</p> <p>AND</p> <p>Patient must have had a forced vital capacity (FVC) greater than or equal to 50% predicted for age, gender and height at the time treatment with this drug for this condition was initiated.</p> <p>AND</p> <p>Patient must have had a forced expiratory volume in 1 second (FEV1)/FVC ratio greater than 0.7 at the time treatment with this drug for this condition was initiated.</p> <p>AND</p> <p>Patient must have had diffusing capacity of the lungs for carbon monoxide (DLCO) corrected for haemoglobin equal to or greater than 30% at the time treatment with this drug for this condition was initiated.</p> <p>AND</p> <p>Patient must not have interstitial lung disease due to other known causes including domestic and occupational environmental exposures, connective tissue disease, or drug toxicity.</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised treatment for this condition.</p>
Prescriber Instructions	<p>A multidisciplinary team is defined as comprising of at least a specialist respiratory physician, a radiologist and where histological material is considered, a pathologist. If attendance is not possible, because of geographical isolation consultation with a multidisciplinary team is required for diagnosis.</p> <p>Application for of initial treatment authorisation must be in writing and must include:</p> <ol style="list-style-type: none"> 1. A completed authority prescription form 2. A completed IPF Authority Application Supporting Information Form; and 3. A signed patient acknowledgement. <p>Patient must not have an acute respiratory infection at the time of FVC testing.</p>
Administrative Advice	<p>Special Pricing Arrangements apply.</p> <p>No increase in the maximum quantity will be authorised</p>

Public Summary Document – November 2016 PBAC Meeting

	<p>No applications for increased repeats will be authorised</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Prior Written Approval of Complex Drugs Reply Paid 9826 GPO Box 9826 HOBART TAS 7001</p>
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Flow on changes to the listing for nintedanib: include additional criterion “The treatment must be the sole PBS-subsidised treatment for this condition” and include additional restriction “Initial 2: change or re-commencement of treatment” to allow for switching between the nintedanib and pirfenidone.