5.12 PIRFENIDONE 267 MG CAPSULE, 270, ESBRIET®, ROCHE PRODUCTS PTY LTD.

1 Purpose of Application

1.1 Authority required listing (initial treatment: section 100 – HSD; continuing treatment: section 100 – HSD (Community Access) or Section 85) for pirfenidone for treatment of idiopathic pulmonary fibrosis (IPF). The submission proposed that only the initial listing be under the affiliation of a specialist hospital unit and following the establishment of an accurate IPF diagnosis via a multidisciplinary team, prescribing and dispensing can occur in the community.

1.2 Accurate diagnosis of IPF is important as some treatments (eg corticosteroids) can be harmful. The multidisciplinary team described in the Prescriber instruction in the restriction needs careful consideration as to whether it is sufficiently detailed to prevent misdiagnosis.

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
PIRFENIDONE Capsule 267 mg, 270	1	5	$	Esbriet®	RO

Category / Program	~~Section 100 – Highly Specialised Drugs Program~~ GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	-
Severity:	-
Condition:	Idiopathic pulmonary fibrosis
PBS Indication:	-
Treatment phase:	Initial treatment
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☐Streamlined
Treatment criteria:	*Patient must be treated by a respiratory physician or specialist physician experienced in the management of patients with idiopathic pulmonary fibrosis.*

Clinical criteria: *(To be finalised)*	*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 or greater than 50%* *AND* *Patient must have percent predicted carbon monoxide diffusing capacity (DL_{CO}) equal to or greater than 30%.*
Population criteria:	*Patient must be aged 40 years or older.*
Prescriber Instruction 1 *(To be finalised)* **Prescriber Instruction 2**	*Consultation with a multidisciplinary team may be necessary in the diagnosis of idiopathic pulmonary fibrosis (IPF). The multidisciplinary team may comprise of at least a pulmonologist, radiologist and where required, pathologist.* *Authority applications for initial treatment must be made in writing and must include:* *(a) a completed authority prescription form; and* *(b) a completed IPF Initial PBS authority application form which includes:* *(i) a copy of the high-resolution computed tomographic scan 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%* *AND* *(iii) a copy of the percent predicted carbon monoxide diffusing capacity (DL_{CO}) equal or greater than 30%.*
Administrative Advice 1 **Administrative Advice 2**	*No applications for increased maximum quantities will be authorised.* *No applications for increased repeats will be authorised.* *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).* *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* *Applications for authority to prescribe should be forwarded to:* *Department of Human Services* *Prior Written Approval of Complex Drugs* *Reply Paid 9826* *HOBART TAS 7001*
Cautions	-

Category / Program	~~*Section 100 – Highly Specialised Drugs Program (Community Access)*~~ GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives

Episodicity:	-
Severity:	-
Condition:	Idiopathic pulmonary fibrosis
PBS Indication:	Idiopathic pulmonary fibrosis
Treatment phase:	Continuing treatment
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☒Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☐Streamlined
Treatment criteria:	*Must be treated by a respiratory physician or specialist physician experienced in the management of patients with idiopathic pulmonary fibrosis.*
Clinical criteria: *(To be finalised)*	*Patient must have previously received PBS subsidised treatment with this drug.*
Population criteria:	*Patient must be aged 40 years or older.*
Prescriber Instructions	
Administrative Advice 1 **Administrative Advice 2**	*No applications for increased maximum quantities will be authorised.* *No applications for increased repeats will be authorised.* *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).* *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* *Applications for authority to prescribe should be forwarded to:* *Department of Human Services* *Prior Written Approval of Complex Drugs* *Reply Paid 9826* *HOBART TAS 7001*
Cautions	-

Category / Program	~~*Section 100 – Highly Specialised Drugs Program (Community Access)*~~ GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	-
Severity:	-
Condition:	Idiopathic pulmonary fibrosis
PBS Indication:	Idiopathic pulmonary fibrosis
Treatment phase:	*Initial PBS-subsidised treatment* (grandfather patient)

Restriction Level / Method:	☐ Restricted benefit ☒ Authority Required - In Writing ☒ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☐ Streamlined
Treatment criteria:	*Must be treated by a respiratory physician or specialist physician experienced in the management of patients with idiopathic pulmonary fibrosis.*
Clinical criteria *(To be finalised)*	*Patient must have received non-PBS subsidised treatment with this drug prior to [listing date]*
Population criteria:	Patient must be aged 40 years or older.
Prescriber Instructions	-
Administrative Advice 1	*No applications for increased maximum quantities will be authorised.* *No applications for increased repeats will be authorised.*
Administrative Advice 2	*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).* *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* *Applications for authority to prescribe should be forwarded to:* *Department of Human Services* *Prior Written Approval of Complex Drugs* *Reply Paid 9826* *HOBART TAS 7001*
Cautions	-

2.2 The submission sought listing on the basis of a cost utility analysis (CUA) comparing pirfenidone to best supportive care (BSC).

2.3 The submission proposed a Special Pricing Arrangement (SPA) with [redacted]% rebate on the ex-manufacturer price for pirfenidone. This equated to an effective dispensed price for the maximum quantity (pirfenidone 267 mg x 270 capsules) of $[redacted] in public hospitals and $[redacted] in private hospitals. In addition, the submission indicated that the expiry of the pirfenidone patent in Australia is of further relevance to the requested price. Following TGA approval, the sponsor anticipates that a data exclusivity period of 5 years will apply to pirfenidone prior to generic competition. The submission assumed that a price reduction of 47.4% will apply to pirfenidone following this period, consistent with the average reduction due to price disclosure claimed in the Medicines Australia 2015-16 Federal Government Budget submission. This price reduction is incorporated into the economic evaluation. Given that the submission has not included any commitment to mandate this price reduction 5 years post listing, the incorporation of this factor in the economic evaluation was considered by the evaluator to be highly inappropriate. The extent of competition that will exist in the IPF market following the introduction of generics and following impacts on price disclosure cannot be predicted with certainty. Consequently, the exclusion of this price reduction from the economic model was necessary with a revised based case being presented (refer to Economic analysis below). The ESC agreed this is appropriate and the price reduction should not be factored in to the economic evaluation.

2.4 Clinical criteria for ongoing therapy is limited to patients who have previously received PBS subsidised treatment or non-PBS subsidised treatment prior to listing. Consequently, once initiated on treatment, there is the potential for therapy to occur indefinitely. While this is consistent with the submission's claim that chronic treatment will occur in clinical practice, it should be noted that the recent update to the American Thoracic Society (ATS) clinical practice guidelines for IPF (Raghu 2015) states that the current available evidence for pirfenidone does not allow suggestions about the optimal duration of therapy, and it is unknown how long treatment effect endures with ongoing therapies.

2.5 The ESC discussed the difficulty of having a continuation rule for IPF treatment based on response. The purpose of treatment is to prevent progression of the disease, as once patients progress there can be no further gains in lung function. There is no way to know if patients are responding to treatment, only that they are not getting worse.

2.6 The requested restriction has not specified whether pirfenidone should be used as sole therapy for the treatment of IPF. Combination treatment was not permitted in the pivotal trials. Given the complex pathology of IPF, combination treatment with nintedanib and pirfenidone has been suggested in the literature as a possible future regimen for patients with definite or probable IPF (Wuyts 2014, Wells 2015). The ESC considered that the combination of nintedanib and pirfenidone is not supported by clinical evidence and a note should be added to the Cautions in the PBS listing to advise prescribers that the combination should not be used.

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

3 Background

3.1 The first round clinical evaluation report from the TGA was received just after the ESC meeting in October 2015. The submission was made under the TGA/PBAC Parallel Process, with the delegate's consideration expected in January 2016.

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 (median survival: 3 to 5 years), causing a progressive decline in lung function, which increasingly restricts routine physical activity due to disrupted alveolar-capillary barrier architecture, leading to impaired gas exchange. No medications are listed on the PBS specifically for the treatment of IPF.

4.2 The submission proposed that pirfenidone be given concomitantly with BSC for the treatment of IPF.

5 Comparator

5.1 The submission nominated BSC as the main comparator. The ESC considered this was appropriate.

5.2 The submission stated that the sponsor was aware that nintedanib, another novel agent for the treatment of IPF, was considered by the PBAC at the March 2015 meeting. Although this agent has yet to be TGA approved or PBS listed, the submission included nintedanib as a supplementary comparator on the basis that it is also used for the treatment of patients with IPF.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (48), health care professionals (4) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described the benefits of treatment with pirfenidone in patients with IPF in slowing down the progression of IPF and improving the quality of life. The comments also requested the PBAC eligibility for the drug include patients with FVC <50% because the patients with FVC 40-50% may still be functional, though they were excluded from clinical trials. It was further commented that confirmation of diagnosis via a designated tertiary hospital would make it difficult to access the drug for respiratory physicians working outside the metropolitan areas.

6.3 The PBAC noted the advice received from Lung Foundation Australia, Department of Respiratory and Sleep Medicine, RPA hospital NSW, and Department of Respiratory Medicine, Eastern Health Victoria clarifying the likely use of pirfenidone in clinical practice. The organisations provided advice in support of PBS listing given the anti-fibrotic treatments improve the prognosis for patients, with The Lung Foundation noting these drugs been shown to alter the natural history of IPF. However, Department of Respiratory and Sleep Medicine, RPA hospital NSW stated that 20% of patients referred to the Australian IPF Registry were over-diagnosed with IPF. Thus, it was strongly recommended to restrict this medication to specialist centres only, where an accurate IPF diagnosis could be made via specialist interstitial lung disease (ILD) multidisciplinary team. This would enable controlled prescription to patients with accurate IPF diagnosis and prevent over-prescription by non-ILD specialists.

6.4 The PBAC noted that this advice was supportive of the evidence provided in the submission.

Clinical trials

6.5 The submission was based on three head-to-head trials comparing pirfenidone to placebo: ASCEND (n=555), CAPACITY-2 (n=435) and CAPACITY-1 (n=344).

6.6 Details of the trials presented in the submission are provided in the table below.

Table 1: 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.	22 May 2014
	King Jr TE, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis.	*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.	June 2009
	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.	June 2009
	Noble PW, Albera C, Bradford WZ, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): Two randomised trials.	*The Lancet*. 2011; 377(9779): 1760-1769
	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).	*American Journal of Respiratory and Critical Care Medicine. 2010; 181(1)*
	Sahn SA, Albera C, Du Bois RM, et al. Clinical outcomes with pirfenidone therapy in Treatment-adherent (TA) patients with Idiopathic Pulmonary Fibrosis (IPF).	*American Journal of Respiratory and Critical Care Medicine. 2010; 181(1)*
	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.	*American Journal of Respiratory and Critical Care Medicine. 2010; 181(1)*
	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.	*American Journal of Respiratory and Critical Care Medicine.* 2011; 183(1)

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

6.7 The key features of the direct randomised trials are summarised in the table below.

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
ASCEND	555	R, DB, MC, MN, phase III; 52 weeks	Low	IPF	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	R, DB, MC, MN, phase III; 72 weeks	Low	IPF		
CAPACITY-1	344					

Abbreviations: MC = multicentre; DB = double blind; MN = multinational; R = randomised; FVC%Pred = forced vital capacity percent predicted; IPF = idiopathic pulmonary fibrosis. *Results from CAPACITY-2 were limited to the 2403mg per day group as this was consistent with the proposed dosage in the draft PI. ^ 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. Source: compiled during the evaluation

6.8 Results from CAPACITY-1 and 2 were known prior to the planning of ASCEND. While many aspects of the trial design for ASCEND were similar to the CAPACITY trials, key differences were observed in the following areas:

- Trial duration: 52 weeks for ASCEND compared to 72 weeks in CAPACITY.
- Inclusion criteria from CAPACITY was adjusted in ASCEND to include IPF patients with a lower DL_{CO}, higher FEV_1/FVC ratio and longer time since diagnosis. The CSR for ASCEND indicated that changes to the inclusion criteria were done with the intent of recruiting patients with a greater risk of disease progression. These differences are reflected in the comparison of disease state characteristics, with reduced measures of pulmonary function (ASCEND vs CAPACITY: FVC%Pred: 67.8-68.6% vs 73.1-76.2% and DL_{CO}: 43.7-44.2% vs 46.1-47.8%) and longer time since IPF diagnosis (ASCEND vs CAPACITY: 1.7 years vs 1.1-1.3 years) reported in ASCEND. This is of consequence to the exchangeability of the pirfenidone trials.
- Secondary endpoints: key secondary endpoints were revised in ASCEND, with change from 6 minute walk test (6MWT) distance introduced; definition of progression free survival (PFS) changed (substitution of DL_{CO}≥15% increase for 6MWT≥50m decrease; FVC%Pred≥10% decrease retained); and the removal of time to worsening of IPF (included the assessment of acute IPF exacerbation).

6.9 The above observations do not imply that it was unreasonable to update the ASCEND trial design, given the expectation that investigators would incorporate advancements in the understanding of IPF disease progression. Nevertheless, there is the potential risk that prior knowledge of results from CAPACITY (refer to Table 3 below) influenced the selection of patients, outcome factors and analyses with the view of increasing the observed treatment effect associated with pirfenidone. The adjustments to trial duration and secondary endpoints in ASCEND were of particular consequence to the pre-specified time to event meta-analyses presented by the submission:

- Censoring of data from CAPACITY-1 and 2 to allow a 52-week comparison in the meta-analyses had profound impact on the estimated treatment effect for overall survival (refer to Comparative effectiveness below).
- PFS was primarily driven by 6MWT≥50m decrease. While a relationship between 6MWT and survival has been observed in an IPF clinical trial investigating

interferon ɣ-1b (du Bois 2014), the submission does not present any evidence regarding the formal validation of PFS as an appropriate composite outcome measure for IPF. In addition, no pirfenidone trial based analyses were presented to indicate whether any relationship with OS could be reliably determined or quantified.

6.10 The ESC noted the additional information provided in the PSCR (p2) where the baseline values for key physiological measures of disease status were overlapping across the individual studies, supporting the similarities between trial populations and pooling of data across ASCEND, CAPACITY-2 and CAPACITY-1. Overall, the ESC concluded that there is a reasonable similarity between patients in these studies.

Comparative effectiveness

6.11 Section B-DRT of the submission relied solely on the presentation of the results of the meta-analyses (ASCEND, CAPACITY-2 and CAPACITY-1). Although the submission claims that results from the pooled analysis are a single, stable and robust estimate, this can only be comprehensively evaluated through the concomitant examination of the individual trial results. Given the likely non-exchangeability of the trial participants and the potential impact of censoring on the observed treatment effect (refer above); this necessitates the concomitant examination of the individual trial results. Key results for the primary outcome (change in FVC%Pred; FVC%Pred response), clinically relevant outcomes (OS, time to worsening of IPF) and variables directly used in the economic evaluation (PFS) are presented in the table below.

Table 3: 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	[redacted]	[redacted]
		CAPACITY-2		
	To week 52	CAPACITY-1		[redacted]
		CAPACITY-2		
		ASCEND		
FVC%Pred response - decline of ≥10% to 0%; RR (95% CI)	To week 52	CAPACITY-1		[redacted]
		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)	
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(a).2.1, p5, Table B(a).3.1, p8, Supplementary appendix to Section B of the submission; Table 11, p68, Tables 2.1-3, 2.1-4, p313-332; Table 4.1-1, p467-471, 2014 Resubmission integrated summary of efficacy; Table 25-26, p84-87, Table 14.2.1-6, p543, Table 14.2.2-15, p592, Table 14.2.2-11, p588, Table 14.2.2-7, p584, ASCEND CSR; Table 11-9, p132, Table 14.2.1-1, p518, Table 14.2.2-1, p563, CAPACITY-1 CSR; Table 11-9, p140, Table 14.2.1-1, p561, Table 14.2.2-1, p603, CAPACITY-2 CSR; Table 8, p21 of FDA- pirfenidone cross discipline team leader review; Table B.6.4, p49, Section B-DRT; Table 7-22, p134, Table 7-29, p146, Integrated summary of effectiveness 2009

6.12 While statistically significant differences were observed in ASCEND and CAPACITY-2 for the primary efficacy analysis of mean change from baseline FVC%Pred at week 52 and 72, results from CAPACITY-1 did not reach significance, with the point estimates (week 72: 0.6%; week 52: 1.9%) unlikely to be clinically significant. In addition, considerable variability across the placebo arms (week 52: -[redacted]% to -[redacted]%; week 72: -[redacted]% to -[redacted]%) brought into question the comparability of the trial populations.

6.13 In regard to overall survival, although the base case analysis (cut-off at 52 weeks) indicated statistically significant benefits in favour of pirfenidone (HR = 0.52%, 95% CI: 0.31, 0.87), the vital status-end of study exploratory analysis reported in the FDA cross discipline team leader review for pirfenidone (located during the evaluation) reported non-significant differences (HR = 0.75, 95% CI: 0.50, 1.11). The review considered that vital status-end of study survival analysis more appropriately informed the efficacy of a drug with respect to disease modification/survival. The ESC noted that the PSCR (p3) addressed this issue and argued that the totality of evidence has been accepted by the FDA and EMA, and further that a recent NEJM[1] editorial indicates acceptance of FVC as a surrogate for mortality.

6.14 A brief summary of results from the indirect comparison with nintedanib is provided in the table below. Although no statistically significant differences were observed across the analyses, the reliability of the indirect comparison was limited by the lack of exchangeability for the trial populations (FVC%Pred at baseline: ASCEND: 68%; Trial 32 and 34: 78-81%).

Table 4: 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)	[redacted]
All-cause mortality	HR (95% CI)	[redacted]
IPF-related mortality	HR (95% CI)	[redacted]

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

6.15 Although the reduction in FVC in the placebo groups of the pirfenidone studies are similar, as noted in the FDA report in the NEJM (see figure below), it is important to note that the CAPACITY studies were over 72 weeks and the ASCEND over 52 weeks, the same as nintedanib. The ESC considered it clear that the pirfenidone

[1] 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

studies recruited patients with more accelerated decline in FVC than the nintedanib studies, especially the ASCEND study.

Analysis of Forced Vital Capacity and All-Cause Mortality.*

Study	Forced Vital Capacity			All-Cause Mortality		
	Change from Baseline (ml)		Treatment Difference (95% CI)	No. of Deaths (%)		Hazard Ratio for Time to Death (95% CI)
	study drug	*placebo*		*study drug*	*placebo*	
Pirfenidone study 2 (November 2008)	−318	−475	157 (3 to 311)	14 (8.0)	20 (11.5)	0.65 (0.33 to 1.29)
Pirfenidone study 3 (November 2008)	−379	−373	−6 (−178 to 167)	18 (10.5)	17 (9.8)	1.07 (0.55 to 2.08)
Pirfenidone study 1 (re-submitted; February 2014)	−235	−428	193 (96 to 289)	12 (4.3)	21 (7.6)	0.57 (0.28 to 1.16)
Nintedanib study 1 (June 2010)	−60	−191	131 (27 to 235)	7 (8.1)	9 (10.3)	0.73 (0.27 to 1.98)
Nintedanib study 2 (October 2013)	−115	−240	125 (78 to 173)	13 (4.2)	13 (6.4)	0.63 (0.29 to 1.36)
Nintedanib study 3 (October 2013)	−114	−207	94 (45 to 143)	22 (6.7)	20 (9.1)	0.74 (0.40 to 1.35)

* The studies are listed in chronologic order by drug, with study numbers as referenced in the product labels and the months in which enrolment ended. Data for forced vital capacity are the absolute values for the change from baseline to week 52 for pirfenidone study 1, to week 72 for pirfenidone studies 2 and 3, and to week 52 for all nintedanib studies; the change from baseline for pirfenidone studies was based on descriptive statistics, and the change from baseline for nintedanib studies was based on regression analysis. Mortality data are from the vital status analysis (from randomization to the time of death) and include all deaths irrespective of the cause and of whether the patient had continued treatment. Hazard ratios for time to death are based on Cox proportional-hazards regression analysis. CI denotes confidence interval.

Source: 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):p 1190.

6.16 During the evaluation, results from a network meta-analyses published by Loveman 2015[2] were located. While pirfenidone and nintedanib demonstrated beneficial effects, the authors concluded that nintedanib appeared to have a superior benefit for slowing decline in FVC (OR = 0.67, 95% CI: 0.51, 0.88).

6.17 The ESC considered that the data from the meta-analysis, by Loveman 2015, is valuable in not only providing another approach to the meta-analysis of the data and reassurance that the trials had similar patients but suggesting that pirfenidone is inferior to nintedanib, with respect to slowing the decline in FVC. The ESC noted in the review by Loveman 2015, there is conflicting data where pirfenidone has a trend to better overall survival but nintedanib has a trend to better prevention of exacerbations.

[2] Loveman E, Copley VR, Scott DA, Colquitt JL, Clegg AJ and O'Reilly. Comparing new treatments for idiopathic pulmonary fibrosis-a network meta-analysis. BMC Pulmonary Medicine, 2015; 15:37.

Comparative harms

6.18 Key results from the meta-analyses of safety outcomes are presented in the following table.

Table 5: Summary of the meta-analyses of key safety outcomes from the pirfenidone trials

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

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

* It appears 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 is 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

6.19 In terms of common adverse events (>5%), 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. Significant reductions were observed for IPF and peripheral oedema.

Benefits/harms

6.20 A summary of the comparative benefits and harms for pirfenidone versus placebo is presented in the table below.

Table 6: 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	[redacted]	173	-6.9	[redacted]	[redacted]
CAPACITY-2	174	-4.4	[redacted]	174	-9.2	[redacted]	
ASCEND	278	[redacted]	[redacted]	277	[redacted]	[redacted]	

Harms^						
	Pirfenidone	**Placebo**	**RR (95% CI)**	**Event rate/100 patients***		**RD% (95% CI)**
				Pirfenidone	**Placebo**	
Photosensitivity reaction						
ASCEND, CAPACITY-1 & 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash						
ASCEND, CAPACITY-1 & 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stomach discomfort						
ASCEND, CAPACITY-1 & 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

6.21 On the basis of direct evidence presented by the submission, in comparison to placebo, pirfenidone was associated with:

- Approximately a 4.0% reduction in absolute change in forced vital capacity percent predicted (FVC% Pred) from baseline to week 52.
- Insufficient evidence to support a significant difference in OS.

6.22 On the basis of direct evidence presented by the submission, for every 100 patients treated with pirfenidone in comparison to placebo:

- Approximately 8 additional patients would have a photosensitivity reaction over 52-72 week duration of follow-up.
- Approximately 20 additional patients would have a rash over 52-72 week duration of follow-up.
- Approximately 6 additional patients would have stomach discomfort over 52-72 week duration of follow-up.

Clinical claim

6.23 The submission described pirfenidone as having a superior efficacy profile when compared with placebo in patients with IPF. While the evidence appears to broadly point towards superiority in terms of efficacy, the claimed treatment effect across the

pooled analyses is likely to be unreliable, especially for the patient relevant outcomes of OS and acute IPF exacerbations, given the following reasons:

- Exchangeability of the pirfenidone trial populations: the recruitment of patients in ASCEND with a greater likelihood of disease progression and substantial variability across the placebo arm response rates for FVC%Pred are indicative of the lack of consistency in the IPF populations of the pivotal trials.
  - The PSCR (p. 1) argued that: the trials were similar in design, eligibility criteria, patient population, intervention and comparator, and that pooling of data has been considered acceptable by other regulatory authorities (e.g. EMA); differences in inclusion criteria such as time since diagnosis are minor and not clinically significant. The ESC noted that the overall effect in the pooled analysis is driven by the ASCEND study which was planned in response to the rejection by the FDA on the basis of CAPACITY 1 and 2. Careful selection for the ASCEND study is reflected in the fact that of 1,562 screened patients, 1,007 were excluded because of exclusion criteria. However, the ESC further noted the information provided in Figure 1 of the PSCR and considered there is reasonable similarity between patients in the three studies.
- Inconsistencies across the results of the individual pirfenidone trials: while statistically significant differences for the primary outcome of change in FVC%Pred were observed in ASCEND and CAPACITY-2, this was not achieved in CAPACITY-1.
  - The PSCR (p2) explained why the primary endpoint was not met including that a significant imbalance was observed resulting in a higher proportion of patients trending towards borderline obstructive disease in the CAPACITY-1 placebo arm. The PSCR further notes that due to the inconsistency in results of the primary outcome in the CAPACITY trials, a third phase III trial (ASCEND) was requested by the FDA to confirm the efficacy of pirfenidone in patients with IPF, and was specifically designed to exclude patients with borderline obstructive disease. ESC considered pirfenidone appeared effective in relation to change in FVC%Pred, but not exacerbations.
- Reliability of the base case estimate of OS (cut-off at 52-weeks): vital status – end of study analysis (preferred for the demonstration of efficacy) presented in the FDA cross discipline team leader review did not demonstrate statistically significant benefits for survival.
  - The PSCR (p3) argued that it may not be appropriate to rely on this analysis and presented evidence that the FDA has accepted FVC as a surrogate for mortality in IPF. The ESC noted the significance of the OS outcomes depended on the analysis chosen; the FDA[3] had reported the preferred analysis for OS is the vital status analysis which is not significant. The submission used the on-treatment analysis, preferred for safety analyses, to support a significant difference in OS: vital status: 0.75 (0.50,1.11) vs on-treatment: **0.52 (0.31, 0.87).**
- No formal validation of PFS as an appropriate composite outcome in IPF; the submission did not provide any evidence to quantify the relationship between PFS and OS noting that the definition was changed from that used in the CAPACITY trials to increase the projected event rate. The PSCR (p. 3) noted that the submission does not make the claim that PFS is a surrogate for OS in IPF.

[3] 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

- Assessment of acute IPF exacerbations was limited to the CAPACITY trials within the composite outcome measure of time to worsening of IPF. No statistically significant differences were observed.

6.24 The submission described pirfenidone as having an acceptable safety profile when compared with placebo in patients with IPF. Although the adverse event profile of pirfenidone is well established with up to 10 years post-marketing experience, the direct evidence presented by the submission indicated significantly increased risks in several items across system organ classes. Given the lack of trial based utilities the impact of these adverse events on health related quality of life is not certain. Consequently, the ESC agreed that the evidence would more reasonably support a claim of inferiority in terms of safety.

6.25 The ESC considered that the pirfenidone is superior in efficacy to placebo and has an inferior safety profile.

6.26 The PBAC agreed with the ESC's conclusion.

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

Economic analysis

6.27 The submission presented a modelled economic evaluation using a cost utility analysis. The RSA proposed by the sponsor was incorporated into the economic evaluation. The ESC considered the assumed price reduction of 47.4% after year 5, due to generic competition, should not have been factored in to the economic evaluation.

Table 7: Summary of model structure and rationale

Component	Summary
Time horizon	16 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	Kaplan-Meier plots to 2 years for OS with BSC alone, followed by digitised information from Strand 2014 with Weibull function fitted from 6.2 to 16 years. Pooled Kaplan-Meier plots to 6.2 years for OS with pirfenidone followed by mortality risk of BSC (Weibull function from Strand 2014). For PFS, pooled Kaplan-Meier plots to median of 16 months followed by log-normal model to 16 years. Time on treatment with pirfenidone to 16 years from extrapolation of pooled Kaplan-Meier data for discontinuation of treatment in clinical trials.
Health states	PFS, progression, lung transplant, death
Cycle length	3 months
Transition probabilities	Pirfenidone: Kaplan-Meier data for OS, PFS and time on treatment and parametric model extrapolation to 6.2 years, followed by fitted function from Strand 2014 (same as mortality risk for BSC) to 16 years BSC: Kaplan-Meier data for OS and extrapolation using Strand 2014; and Kaplan-Meier data for OS, and Kaplan-Meier data for PFS plus parametric extrapolation to 16 years.

Source: compiled during the evaluation

6.28 Key drivers of the model are described in the table below. The key driver is OS. This is determined by the submission's approach to translation issues (extrapolation) including an assumption that 16 years is an appropriate time-horizon and extrapolation methods based upon doubtful statistical significance of the secondary

outcome of OS at 52 weeks, and further extrapolation from the open-label extension study which is likely to have produced biased results. The impact of this driver is high and favours pirfenidone.

6.29 The ESC noted that the modelling of OS in the BSC arm is partitioned into three parts (1) KM data from the pooled trials to 2 years, (2) KM data from Strand 2014 to 6.2 years and (3) Weibull extrapolation of the Strand 2014 digitised KM data to 16 years. The main issue with this is the historic data from Strand 2014 may underestimate BSC compared with BSC in the trials, therefore over-estimating the benefit from pirfenidone.

6.30 The ESC noted the key issues on the extrapolation of time on-treatment with pirfenidone is that the data from the trial does not take account of reason for discontinuation, which means that it may over-estimate continuation on treatment beyond the trial; however, equally it may not be reasonable to assume continued efficacy and therefore same discontinuation rates over years 7-16 as in years 0-6.

Table 8: Key drivers of the model

Description	Method/Value	Impact
Time horizon	16 years; assumed from pooled data of 52-72 weeks, and an extension study to 6.2 years followed by fitted parametric functions to 16 years	High, favours pirfenidone
Extrapolation of OS	Pirfenidone: Between 2-6.2 years, OS estimates are derived from a biased source (RECAP extension study); BSC: Beyond 2 years, the OS projection for BSC patients relies upon historical data (Strand 2014) that may underestimate survival for BSC.	High, favours pirfenidone
Time on treatment	Discontinuation rates from pooled data to 6.2 years which appears not to have adjusted for discontinuation due to death when applied to the model	High, favours pirfenidone
The utility of Progression	Sourced from the literature	Moderate, favours pirfenidone

Source: compiled during the evaluation

6.31 The ESC noted issues with the costing of adverse events and exacerbations which are effectively captured in costs of hospitalisations and taken from the trial data. The key issue is that the average length of stay (ALOS) in the pirfenidone arm is half that of the BSC arm, but the rate of hospitalisation is the same. This raises concerns about whether it is appropriate to adjust the DRG costs for differences in ALOS.

6.32 The results of the stepped economic evaluation are provided in the table below. Given the lack of difference in ICERs between steps 2 ($[redacted]) and 8 ($[redacted]), steps 3 to 7 (incorporation of medical resource utilisation (MRU) costs, AE costs, lung transplant costs and end of life costs) are not presented. The application of utilities was considered a separate step by the submission, but the submission noted that the weighting of life years to determine QALYs occurred at each step of the model.

Table 9: Results of the stepped economic evaluation

Step and component	Pirfenidone	BSC	Increment †
Step 1: trial-based costs and outcomes			
Costs	$	$0	$
QALY			
Incremental cost/extra QALY gained			**$** ***($*** ***)***
Step 2: modelled evaluation (extrapolation beyond clinical trials)			
Costs	$	$0	$
QALY			
Incremental cost/extra QALY gained			**$** ***($*** ***)***
Step 8: modelled evaluation (incorporation of proposed rebate)			
Costs	$	$39,577	$
QALY			
Incremental cost/extra QALY gained			**$** ***($*** ***)***

† Italicised figures exclude submission's anticipated 47% price reduction after 5 years due to generic competition
Source: Excel file "Economic Evaluation.xlsx" accompanying the submission refer worksheet 'Results Table'

6.33 The key limitations that render the ICER uncertain were identified as follows:

- The reliability of the clinical data the model draws upon – as described above (see Comparative effectiveness and Clinical claim), there was insufficient evidence to support a survival benefit associated with pirfenidone. The difference between the 52 week and the 72 week data in terms of primary and secondary outcomes is also considered indicative that the comparative effect may not be sustained.
  - The PSCR (p3) argued that the clinical data were appropriate to extrapolate a survival gain over the time frame of the model, and that the approach is conservative because it assumes the same rate of death for BSC and pirfenidone beyond the time frame of the clinical data available. The ESC considered the model remained optimistic in terms of (1) using the 52 week data from CAPACITY 1 and 2, (2) the fact that the BSC arm relies on historical data from Strand 2014 that may not reflect changes in clinical practice in BSC.
- The time horizon in the submission of 16 years is considered overly optimistic in the context of IPF with a median survival of 3-5 years, and given the age of the patients.
  - The PSCR argued (p3) that the median survival should not be used as a basis for considering time horizon because of the long tail, and that in Strand 2014, 17% of the population is alive at 10 years. The ESC considered the key issue with the extrapolation is the assumption of continued benefit beyond the observed difference in the trials and the observed outcomes in the extension study (noting the conservative assumption regarding mortality).
- The open label extension study, RECAP, which contributed the data beyond 2 years to which the parametric survival functions were fitted, was subject to bias in favour of pirfenidone.
  - The PSCR (p3) argued that % of patients who completed CAPACITY 1 and CAPACITY 2 enrolled in RECAP therefore this is unlikely to be subject to healthy cohort bias. However the ESC noted that this does not consider the patients who discontinued during the trials time frame and bias remains an issue.
- The overall implausibility of the model results, which accrued more of the incremental survival gains to the progressive stage of IPF than to the PFS stage.
  - The PSCR (p4) argued that the approach is reasonable and the submission

does not claim PFS is a surrogate for OS or the treatment effect depends on PFS. The ESC considered the use of the Strand 2014 data to extrapolate OS for BSC and the extension study for the pirfenidone arm was an issue. This effectively maximises the difference in OS between the arms. While it is valid that the effect of pirfenidone on PFS and OS can be different, the modelled gains are highly sensitive to the OS assumptions.

- The modelling of discontinuations based on the trial data, which may not take into account discontinuations due to death, has potentially underestimated the cost of pirfenidone in the extrapolation.

6.34 It is reasonable to suggest that progression is associated with increased risk of death. A weakness in the model validity is that changes to definitions of PFS/progression have no impact upon survival. A further illustration of the importance of survival is the effect of varying the time horizon as shown in Figure 1, which plots how the ICER changes with the time horizon. It can be seen that pirfenidone must maintain an effect for over 10 years to achieve an ICER ≤$105,000/QALY. Furthermore, beyond 10 years the ICER tends to plateau with a low gradient.

Figure 1: ICER over the time horizon of model

Source: Constructed during the evaluation

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

Drug cost/patient/year: $

6.35 The estimated usage per patient was based on an expected compliance/adherence rate of %. This was derived from the weighted average daily dose for

pirfenidone observed in ASCEND (n=276; [redacted]mg) and CAPACITY (n=343; [redacted]mg) compared as a percentage to the maximum allowable dose (2403mg). Overall, this resulted in an average [redacted] pirfenidone packs/patient/year.

Estimated PBS usage & financial implications

6.36 This submission was not considered by DUSC. Estimated use and financial implications are presented in the table below.

Table 10: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Incident IPF population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients treated with pirfenidone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pirfenidone packs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net costs to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net costs to MBS	$69,405	$35,614	$36,222	$36,829	$37,434
Net savings to state and territory governments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Overall net cost to government	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**

Abbreviations: IPF = idiopathic pulmonary fibrosis
Source: Table E.2.1, p9-10; Table E.2.2, p11, Table E.5.5, p18, Section E-EPI of the submission

The redacted table above shows that the number of patients treated with pirfenidone is estimated to be less than 10,000 per year at a net cost to the PBS of $30 – $60 million in Year 1 to $100 – $200 million in Year 5.

6.37 The submission relied on a systematic review of IPF incidence rates (Hutchinson 2015), which reported a range of 3-9/100,000 for Europe and North America. The crude average ([redacted]) was applied in the base case of the estimates. While this incidence rate appeared to be comparable to epidemiological studies with larger datasets (n>2000: Navaratnam 2011, Kornum 2008), a recent study by Raghu 2014 using a narrow and broad case definition of IPF reported a 2011 incidence rate of 31.1 and 43.0/100,000 in patients aged ≥65 years, respectively. In comparison to the [redacted] incident IPF patients estimated by the financial model in Year 1, utilisation of the narrow and broad case incidence rate resulted in [redacted] and [redacted] patients, respectively. Given that the estimates from Raghu 2014 are only applicable to patients aged 65 years or older, there is the potential that the incident population may be greater than that predicted by the submission.

6.38 Of further consequence to the reliability of the estimates was the calculation of the prevalent population at year 1, which only included incident patients from the preceding year of PBS listing. As reported in Strand 2014, the median survival for the IPF population was estimated at 4.4 years and 10 year survival was approximately 15%. Given that the expected duration of survival is well beyond 1 year, it would have been more appropriate if the submission applied a broader approach to calculation of the prevalent population at year 1.

6.39 Estimates of net savings due to hospitalisations were considered to be unreliable due to the uncertainty associated with the representativeness of trial based hospitalisations and their applicability to the AR-DRG items (E74A-C). Weighted average length of stay for the AR-DRG items (public/private: 5.7 days) was less that the trial based estimates in the pirfenidone ([redacted] days) and BSC ([redacted] days) arms.

In addition, trends in the costs per day for the AR-DRG items suggested that the incremental difference between pirfenidone and BSC hospitalisation costs (-$[redacted]) was overestimated by the submission.

6.40 Overall, key concerns 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.

Financial Management – Risk Sharing Arrangements

6.41 The sponsor proposed a Special Pricing Arrangement (SPA) in the form of a [redacted]% rebate on the ex-manufacturer price for pirfenidone. The effective prices stated in Section 2 (requested listing) incorporate the RSA.

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

7 PBAC Outcome

7.1 The PBAC decided not to recommend pirfenidone for PBS listing for idiopathic pulmonary fibrosis (IPF) on the basis of unacceptably high and uncertain cost-effectiveness.

7.2 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.

7.3 The PBAC noted the Pre-PBAC response (p2) that the availability of pirfenidone would not increase the frequency of biopsies, contrary to ESC's concern, and that clinician advice is that the 2011 guidelines have led to fewer patients being referred for lung biopsy in Australian clinical practice.

7.4 The PBAC noted the letter received from the Australian IPF Registry Steering Committee (1 July 2015) which endorsed the requirement for a written authority prescription for anti-fibrotic therapy, including the need for diagnosis to have been made at a multidisciplinary team meeting. Such meetings were described by the Steering Committee as likely be held in association with respiratory departments in large public hospitals. The PBAC agreed that a one-off requirement for diagnosis by the multidisciplinary team for initiating therapy would be appropriate.

7.5 The Pre-PBAC response (p2) did not support the use of a continuation rule, and noted that following a FVC decline ≥10% with pirfenidone, continued pirfenidone treatment significantly reduced the risk of death and increased disease stabilisation compared to placebo patients who continued treatment with placebo following a FVC decline ≥10%[4]. The PBAC noted the stopping rule proposed by the National Institute

[4] Nathan SD et al. Effect of Continued Treatment with Pirfenidone Following a Clinically Meaningful Decline in Percent

for Health and Care Excellence (NICE) Guidance for pirfenidone that treatment should be discontinued if there is evidence of disease progression (a decline in per cent predicted FVC of 10% or more within any 12 month period). PBAC considered a future resubmission should explore the likelihood of such a rule proving effective by exploring the numbers of patients who may discontinue treatment based on the clinical trial evidence and the proposed model.

7.6 The PBAC confirmed that best supportive care was the appropriate main comparator for pirfenidone for IPF. Another novel agent for the treatment of IPF, nintedanib, was considered at the same November 2015 PBAC meeting and although not currently PBS listed, nintedanib was considered to be a relevant secondary comparator. 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.

7.7 The PBAC noted the resubmission presented three head-to-head trials comparing pirfenidone to placebo: ASCEND (n=555), CAPACITY-2 (n=435) and CAPACITY-1 (n=344). The Pre-PBAC response (p1) reiterated that the pooled analysis of mortality from ASCEND, CAPACITY-2 and CAPACITY-1 was pre-specified in the statistical analysis plan for ASCEND which was finalised before unblinding.

7.8 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, which was considered by the FDA cross discipline team leader review for pirfenidone to be most representative of the efficacy of a drug in terms of disease modification/survival.

7.9 The FDA review[5] of perfinidone and nintedinab studies suggests that FVC is a valid surrogate for mortality in IPF. This review gave the PBAC more confidence that the lack of statistical significance in OS as reported by the vital status-end of study analysis may be an issue of lack of power in the trials.

7.10 PBAC also 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 as observed.

7.11 Interpretation of the indirect comparison with nintedanib is difficult given the differences in the trial populations and the outcomes. The network meta-analysis

Predicted Forced Vital Capacity in Patients with IPF. Abstract A1016. American Thoracic Society 2015 International Conference, May 15-20, 2015 - Denver.

[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

from Loveman et al 2015[6] suggests 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). However, PBAC considered both drugs are likely to be similarly clinically effective.

7.12 The PBAC did not consider it appropriate to estimate the cost-effectiveness of a medicine for initial PBS listing by including potential future price reductions due to generic competition. This would not be consistent with previous considerations of ICERs and would create major additional uncertainty in the consideration of cost-effectiveness.

7.13 The PBAC noted the model is most sensitive to time on treatment, the time horizon, and the utility of the progression state.

7.14 The cost-effectiveness of the assumed long-term benefit of pirfenidone may be partially supported by effective implementation of the continuation rule described above, as subsidised treatment would not continue for those patients with FVC%Pred deteriorating 10% or more within any 12-month period. The PBAC proposed that the sponsor consider how the use of the continuation rule may impact on the ICER in a future resubmission.

7.15 The 16 year time horizon was considered optimistic in this patient population, and the PBAC noted the figure below signalled a substantial number of patients in both arms remained alive at 10 years (approximately [redacted]% in the placebo arm and [redacted]% in the pirfenidone arm).

[6] Loveman E, Copley VR, Scott DA, Colquitt JL, Clegg AJ and O'Reilly. Comparing new treatments for idiopathic pulmonary fibrosis-a network meta-analysis. BMC Pulmonary Medicine, 2015; 15:37.

Figure 2: Overlay of submission's predicted PFS and OS over 16 years.

Source: Figure D.5.1 of the commentary. Prepared during the commentary from Excel file "Economic Evaluation.xlsx" accompanying the submission.

7.16 The PBAC noted the arguments for the time horizon and extrapolation methods in the Pre-PBAC response (p3), but remained concerned that the modelled survival was unrealistic. Notwithstanding the Pre-PBAC response (p2) discussion on the validity of the Strand data, the PBAC was particularly concerned that the model was sensitive to use of this historical data to extrapolate OS in the BSC arm and that the Strand data may have underestimated BSC compared with BSC in the trials, therefore over-estimating the benefit from pirfenidone.

7.17 The PBAC noted the 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.

7.18 Overall, the PBAC did not consider that the model could be relied upon as a basis for considering the cost-effectiveness of pirfenidone. It recommended that the base case of a modelled economic evaluation in any re-submission should:

- omit potential price reductions associated with any multi-brand competition
- examine the consequences of including a continuation rule reflecting or modified from that proposed in other countries
- reduce the time horizon to 10 years
- revise the extrapolation methods and the post-progression utility so that they no longer overestimate the incremental QALYs gained.

7.19 The PBAC noted that the submission is eligible for an Independent Review.

Outcome:
Rejected

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

Given the high unmet need, Roche is committed to working with the PBAC to provide access at the earliest opportunity to pirfenidone for patients with idiopathic pulmonary fibrosis.