Common Drug Review

Pharmacoeconomic Review Report (Resubmission)

April 2015

Drug	pirfenidone (Esbriet) (267 mg capsules)
Indication	Treatment of mild to moderate idiopathic pulmonary fibrosis in adults
Listing request	As per indication
Manufacturer	Hoffmann-La Roche Limited

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

AE	adverse event
BSC	best supportive care
CDEC	Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
CI	confidence interval
EoL	end of life
EQ-5D	European Quality of Life Scale-5 dimensions
ICUR	incremental cost-utility ratio
IPF	idiopathic pulmonary fibrosis
ITT	intention-to-treat
LoS	length of stay
LY	life-year
QALY	quality-adjusted life-year
SAE	serious adverse event
SGRQ	St. George's Respiratory Questionnaire
WDAE	withdrawal due to adverse event

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Pirfenidone (Esbriet)
Study Question	"An economic evaluation was conducted to estimate the incremental costs and consequences (in terms of LYs and QALYs gained) of pirfenidone for the treatment of mild to moderate IPF, from the perspective of the Canadian public payer."
Type of Economic Evaluation	Cost-utility; cost-effectiveness
Target Population	Adult patients with mild to moderate IPF (from ASCEND and CAPACITY trials)
Treatment	Pirfenidone 267 mg capsules, 3 tabs, TID (2,403 mg/d) plus BSC
Outcomes	QALY
Comparator	BSC, defined as symptom relief, pulmonary rehabilitation, management of comorbidities, and EoL care, including oxygen therapy
Perspective	Publicly funded health care system
Time Horizon	Lifetime time horizon (33 years)
Results for Base Case	$78,024 per QALY for pirfenidone vs. BSC
Key Limitations	• Some model assumptions may favour pirfenidone but were not substantiated by high-quality data (e.g., lower hospital LoS, lower EoL costs with pirfenidone compared with BSC). • The manufacturer's model assumed continued relative efficacy over a patient's lifetime. The majority of incremental benefit accrues after 5 years in the model; however, clinical trial information is available for only a short time frame. • The manufacturer assumed a high rate of discontinuation (50% at 4 years, 85% at 10 years), but an ongoing relative efficacy of pirfenidone vs. BSC. This may favour pirfenidone, as drug acquisition costs are the major cost driver and most of the QALY gains accrue after 5 years. Significant uncertainty exists surrounding discontinuation and relative efficacy.
CDR Estimate	• Based on the assumptions of ○ equal rate of hospitalization and hospital LoS ○ equal EoL costs ○ use of RCT data to inform the first 2 years of survival, ○ the incremental cost per QALY for pirfenidone vs. BSC is $79,758. • Uncertainty in discontinuation and relative efficacy over time: ○ Using the CDR reference case, if there is no further drug discontinuation after 2 years (25%), the incremental cost per QALY for pirfenidone vs. BSC is $136,744. ○ If relative efficacy in the longer term is less than estimated by the manufacturer, the ICUR will be greater.

BSC = best supportive care; CDR = CADTH Common Drug Review; d = day; EoL = end of life; ICUR = incremental cost-utility ratio; LoS = length of stay; LY = life-year; QALY = quality-adjusted life-year; RCT = randomized controlled trial; vs = versus; TID = three times per day.

EXECUTIVE SUMMARY

Background

Pirfenidone (Esbriet) is being reviewed for the management of mild to moderate idiopathic pulmonary fibrosis (IPF) in adults. The recommended dose is 2,403 mg per day (3 × 267 mg capsules three times daily). The confidential price of pirfenidone is $12.77 per capsule or $115 per day.

The CADTH Common Drug Review (CDR) previously reviewed pirfenidone in 2013 for the same indication. At that time, the Canadian Drug Expert Committee (CDEC) recommended that pirfenidone not be listed based on clinical reasons.[1]

The manufacturer submitted a cost-utility analysis (CUA) comparing pirfenidone with best supportive care (BSC; defined as symptom relief, pulmonary rehabilitation, management of comorbidities, and end-of-life [EoL] care including oxygen therapy) in adult patients with mild to moderate IPF, over a lifetime time horizon from the perspective of the health-care payer. Efficacy data for survival and progression of disease were obtained from the ASCEND and CAPACITY trials and the RECAP extension trial for pirfenidone;[2-5] survival for BSC was obtained from an observational study.[6] Mathematical models were used to estimate long-term relative efficacy (survival and progression of disease). Quality of life (QoL) was assigned by mapping health states to St. George's Respiratory Questionnaire (SGRQ) and subsequently to the European Quality of Life Scale-5 Dimensions (EQ-5D) score.

Summary of Identified Limitations and Key Results

Pirfenidone Discontinuation Rates

The manufacturer assumed ongoing discontinuation of pirfenidone over time, such that at four years, 50% of patients were no longer on pirfenidone; this increased to 85% at 10 years (see Appendix 5, Figure 1).

Discontinuation in the studies is due to several reasons that may not be relevant ("... patient's decision, sponsor's decision, lost to follow-up and other reasons" (page 29, manufacturer's report). Further, the CDR clinical expert suggested that discontinuation due to an AE would likely plateau between one year to 1.5 years on treatment. The high discontinuation rate employed by the manufacturer may underestimate drug acquisition costs (the primary cost driver in the model). In addition, it appears that ongoing relative efficacy was assumed even when most patients were no longer taking pirfenidone. This is a major source of uncertainty. If discontinuation remains constant at 25% after two years, the incremental cost per QALY for pirfenidone compared with BSC increases to $124,672 (from the manufacturer's base case of $78,000).

Resource Use Assumptions

Some resource utilization assumptions are not supported by high-quality evidence and appear to favour pirfenidone. These include a length of stay (LoS) for hospitalization episodes that are twice as long for BSC compared with pirfenidone-treated patients, and greater EoL costs for BSC (due to a greater number of patients in this group experiencing IPF-related mortality). Removing these assumptions has only a minor impact on the manufacturer's reference case.

Estimating Short-Term and Long-Term Relative Efficacy

The model used data from an observational trial to inform BSC mortality, and from a randomized controlled trial (RCT) with extension trial data to inform pirfenidone survival. The model-predicted survival is similar to the RCT-predicted survival (over the duration of the RCT), but fitted survival curves were used to estimate long-term survival for both groups. It has not been established that differences in survival persist over a patient's lifetime. This is a key limitation, as the majority of the QALYs (and predicted life-year [LY] gains) occur after five years. If relative efficacy attenuates over time, the ICUR for pirfenidone is likely to be greater.

CDR considered a revised reference case based on:

- RCT data to inform the first two years of survival (instead of a "fitted" curve)
- assumption of no difference in risk or hospitalization LoS
- similar EoL costs.

CDR's revised analysis results in an incremental cost per QALY for pirfenidone compared with BSC of $79,758.

Clinical uncertainty was further assessed with the following scenarios:

- Exploration of uncertainty of discontinuation rates was assessed assuming that the discontinuation rate with pirfenidone would plateau at 25% at two years, resulting in an ICUR of $136,744. Other assumptions led to even greater ICURs (e.g., 15% at 1.5 years results in an ICUR of $143,569).
- If relative efficacy attenuates over time, the true ICUR will be greater.

Conclusions

The manufacturer suggests that pirfenidone is associated with an incremental cost per QALY of $78,000 when compared with BSC. Incremental costs are driven largely by drug acquisition costs, and QALY gains are driven by a predicted survival gain of 2.1 years. Significant uncertainty exists regarding long-term outcomes, including relative efficacy and discontinuation. This is a key consideration, as the majority of the clinical benefit accrues beyond five years. When CDR explored uncertainty using more conservative assumptions regarding discontinuation, the incremental cost per QALY of pirfenidone increased to $137,000 or greater when compared with BSC. If true relative efficacy diminishes over time, the ICUR will also be higher.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted an economic model comparing pirfenidone plus best supportive care (BSC) with BSC alone in a cohort of patients with mild to moderate idiopathic pulmonary fibrosis (IPF) (based on ASCEND/CAPACITY trial participants), based on a health care payer perspective over a patient's lifetime time horizon (33 years).[7] All patients in the model started in the "progression-free" health state and could either remain in this health state or enter the "progressed" health state. The progressed health state was defined using the same definition used in ASCEND: ≥ 10% absolute decline in per cent predicted forced vital capacity (FVC) or ≥ 50 m decline in the six-minute walking test (6MWT) distance. Patients in the progressed health state could transition to the lung transplant health state (only if they were < 70 years old). All health states could transition to the "dead" health state.

Overall survival for pirfenidone-treated patients was estimated by using data from ASCEND/CAPACITY (a 52-week randomized controlled trial [RCT]) and RECAP (an extension trial with up to seven years of follow-up) to create a best-fitting survival curve to model long-term survival.[2-4] Overall survival for the BSC group was obtained from an observational cohort of patients with IPF (321 patients with a median survival of 4.4 years),[6] and best- fitting survival curves were created to estimate long-term survival (Appendix 5, Figure 2). The probability of moving from the non-progressed state to the progressed state was informed by data from ASCEND/CAPACITY (using the definition given above) for both the pirfenidone and BSC groups, and by extrapolating data from the 52-week trials to a lifetime time horizon by fitting a parametric curve (Appendix 5, Figure 3). The probability of a lung transplant did not differ by treatment, and was informed by expert opinion; survival post-lung transplantation was informed by the manufacturer's data.[5]

Preference-based quality of life (QoL) was estimated by extrapolating from a data set of UK IPF patients that included results from both the St. George's Respiratory Questionnaire (SGRQ) and the European Quality of Life Scale-5 Dimensions (EQ-5D); a best-fitting, generalized mixed model was created, accounting for repeated measures and explanatory variables (no reference was provided to the study). Patients were categorized by health state, and the corresponding SGRQ was mapped to the EQ-5D. Pirfenidone discontinuation (due to an adverse event [AE], or patient's or sponsor's decision) from ASCEND/CAPACITY/RECAP was used to create a survival curve for drug use over a lifetime time horizon. Drug costs were obtained from the manufacturer, and the daily dose (including dose reduction and temporary cessation for AE) was obtained from trial data. The probabilities of hospitalization for pirfenidone and BSC were obtained from ASCEND/CAPACITY (SAEs were similar between the two groups). However, it is assumed that average length of stay (LoS) was twice as long in the BSC group (from CAPACITY data); per diem costs were obtained from Statistics Canada. Disease management costs (clinic visits, oxygen, testing) were based on expert opinion and Ontario costs, and were slightly greater with more severe disease. Resource use for lung transplantation (workup, index year, and follow-up costs) was based on expert opinion. EoL costs, differentiated by IPF versus other causes of mortality, were estimated from Canadian data.[8]

2. MANUFACTURER'S BASE CASE

Treatment with pirfenidone resulted in incremental costs of $129,471 compared with BSC, primarily driven by drug acquisition costs (+ $127,625). Treatment with pirfenidone resulted in an additional 1.7 QALYs (2.1 LY), with an ICUR of $78,024 (Table 2).

TABLE 2: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE

	Total Costs ($)	Incremental Cost of Pirfenidone ($)	Total QALYs	Incremental QALYs of Pirfenidone	Incremental Cost per QALY ($)
BSC	56,226		4.05		
Pirfenidone	185,697	129,471	5.71	1.66	78,024

BSC = best supportive care; QALY = quality-adjusted life-year.
Source: Manufacturer's pharmacoeconomic submission.

2.1 Summary of Manufacturer's Sensitivity Analyses

The manufacturer conducted deterministic, one-way, and probabilistic sensitivity analyses. None of the manufacturer's sensitivity analyses resulted in notable changes to the ICUR (range: $72,133 to $84,670). Cost-effectiveness acceptability curves indicated that the probability that pirfenidone would be cost effective at a willingness-to-pay threshold of $50,000 per QALY is approximately 3%; at a willingness-to-pay threshold of $75,000, the probability is 37%; and, at a willingness-to-pay threshold of $100,000, it is 77%.

3. LIMITATIONS OF MANUFACTURER'S SUBMISSION

3.1 Pirfenidone Discontinuation Rate

The model fits a curve of discontinuation rates observed in ASCEND/CAPACITY/RECAP), leading to 60% discontinuation at five years and 85% at 10 years (Appendix 5, Figure 1). The clinical expert suggests that this lacks face validity — most discontinuation due to AE would occur within the first year and would likely stabilize after this time (note that discontinuation at 52 weeks in the RCTs was approximately 14% and was 20% at 72 weeks). Further, it is unclear that discontinuation due to "... patient's decision, sponsor's decision, lost to follow-up and other reasons" (page 29, manufacturer report), as distinct from AEs, reliably estimates real-world use in a funded medication. It is also counterintuitive to assume continued relative efficacy over a lifetime time horizon when only half of the patients remain on the drug at four years. (While not clearly described, the continued separation of the survival curves suggests that ongoing efficacy continues despite a growing proportion of patients no longer receiving the medication.) Given that drug acquisition costs are the main cost driver, and that most of the accrual of QALYs (LYs) occur beyond five years, this assumption may bias in favour of pirfenidone.

3.2 Hospital Length of Stay

The manufacturer selected a finding from the CAPACITY trial that LoS was approximately twice as long for BSC-treated patients (driven by a few BSC patients with very long LoS). Statistical significance is not presented, nor is pooled data from other trials. Further, the risk of hospitalization demonstrated no difference (i.e., the assumption lacks face validity). This assumption favours pirfenidone.

3.3 End-of-Life Costs

The model assumes that EoL costs for death attributable to IPF are greater than for non-IPF death. However, the data used to inform this are not specific to IPF, and cause of death ("organ failure") as defined in the source study may apply to all IPF patients. This may bias in favour of pirfenidone (which has a reported lower risk for IPF-related mortality than BSC).

3.4 Uncertainty in Long-Term Relative Efficacy

The model assumes that differences observed in short-term studies (two years within RCTs) can be extrapolated to a lifetime time horizon. While model validation demonstrates reasonable modelled versus observed mortality over the short term (despite using observational data to inform the BSC strategy), long-term relative efficacy (survival as well as progression) is not known. This is visually apparent in the survival curves created for the model (Appendix 5, Figures 2 and 3). If relative efficacy is less than estimated, the ICUR will be substantially greater.

3.5 CDR Analyses

CDR considered the following analyses to address the limitations identified above:

1. Identical probability of hospitalization (5.22%) and LoS (8.48 days) for both treatment strategies; ICUR = $79,543 for pirfenidone versus BSC.
2. EoL costs similar regardless of cause of death; ICUR = $78,478 for pirfenidone versus BSC.
3. Use of survival data observed from the RCT, followed by parametric survival curves (instead of using the parametric curve for the entire time frame, which may slightly overestimate differences in survival); ICUR = $82,488 for pirfenidone versus BSC.
4. Stabilization of discontinuation rates (with no change in relative efficacy).
    a. 25% discontinuation at two years with no further discontinuation; ICUR = $124,672 for pirfenidone versus BSC.
    b. 20% discontinuation at 1.5 years with no further discontinuation; ICUR = $130,792 for pirfenidone versus BSC.
    c. 15% discontinuation at one year with no further discontinuation; ICUR = $137,230 for pirfenidone versus BSC.
    d. An alternate method to express this would be to attenuate relative efficacy with increasing discontinuation. However, given the use of fitted survival curves, CDR was unable to reliably modify the relative benefit between the two treatments by discontinuation.
5. Short time horizon. To assess the timing of accrual of benefits and costs, shorter time horizons were explored. Note that in the reference case, incremental QALYs and LYs are 1.7 and 2.1, respectively.
    a. Two years: incremental QALY = 0.116; incremental LY = 0.133; ICUR = $462,211 for pirfenidone versus BSC.
    b. Five years: incremental QALY = 0.509; incremental LY = 0.610; ICUR = $188,271 for pirfenidone versus BSC.
    c. Ten years: incremental QALY = 1.122; incremental LY = 1.376; ICUR = $106,941 for pirfenidone versus BSC.

3.5.1 CDR Reference Case

CDR analyses 1 through 3 above examine assumptions that favour pirfenidone, and are used in a plausible reference case analysis. This CDR estimated revised reference case results in an ICUR of $79,758 for pirfenidone compared with BSC.

The assumption used by the manufacturer that led to very high discontinuation rates, along with the assumption of continued treatment efficacy, is uncertain (item 4). Use of more conservative discontinuation rates (in keeping with the opinion of the clinical expert) without modification of relative efficacy estimates greatly increased the ICUR. Using the CDR reference case and a 25% discontinuation at two years with no further discontinuation in the CDR reference case increases the ICUR to $136,744 per QALY for pirfenidone versus BSC. Use of lower discontinuation rates (20% at two years, 15% at 1.5 years) led to even greater ICURs ($143,569 and $150,593, respectively).

Price reduction was assessed in both the manufacturer's base case and CDR reference cases examining the uncertainty of discontinuation (25% discontinuation at two years with no further discontinuation) (Table 3), where a price reduction of 50% would render the ICUR less than $70,000 in the CDR reference case.

TABLE 3: CDR REANALYSIS OF PRICE REDUCTION SCENARIOS

ICURs of pirdenidone versus BSC		
Price	**Base-Case Analysis Submitted by Manufacturer ($)**	**CDR Reference Case Plus Discontinuation 25% at 2 Years With No Further Discontinuation ($)**
Submitted	**78,024**	**136,744**
10% reduction	70,333	123,370
20% reduction	62,642	109,996
30% reduction	54,951	96,622
40% reduction	47,260	83,248
50% reduction	39,569	68,874
60% reduction	31,878	56,500
70% reduction	24,186	43,126
80% reduction	16,495	29,752
90% reduction	8,804	16,378

CDR = Common Drug Review; ICUR = incremental cost-utility ratio.

4. ISSUES FOR CONSIDERATION

Pirfenidone is indicated for mild to moderate IPF, but potentially its use may be continued or initiated in severe disease. The clinical expert suggested that in patients who do not respond ("progressors"), the drug may be stopped; however, it is not clear that patients clearly demarcate into responders and non-responders, or whether this practice would be accepted if pirfenidone were reimbursed.

4.1 Patient Input

Patients report the significant impact IPF has on their quality of life (QoL), activities of daily living, and productivity, particularly as the disease progresses. QoL, including QoL with progressed disease, is incorporated into the model. A societal perspective was assessed in the sensitivity analysis that included patient-borne oxygen costs (workforce productivity was not included given the average age of 67 years in trials); the results of this sensitivity analysis were similar to the manufacturer's base case. No other proven effective therapy for this condition currently exists.

5. CONCLUSIONS

The manufacturer's base case suggests that pirfenidone results in an additional 1.7 QALYS (largely due to differences in survival of 2.1 LYs) compared with BSC; however, it is $129,000 more costly, driven primarily by pirfenidone's drug acquisition costs. The manufacturer's stated ICUR is $78,000.

The revised CDR reference case does not differ dramatically from the manufacturer's base case. However, there is significant uncertainty in the model, particularly surrounding long-term relative efficacy, as well as discontinuation rates. If true relative efficacy is less than estimated, the ICUR will be higher. This is an important consideration, given that the majority of the clinical benefit accrues beyond five years.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 4 have been deemed appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may also be devices or procedures. Costs are the manufacturer's list prices, unless otherwise specified.

TABLE 4: COST COMPARISON TABLE FOR PIRFENIDONE

Drug/ Comparator	Strength	Dosage Form	Price[a] ($)	Recommended Use	Average Cost per Year ($)
Pirfenidone (Esbriet)[a]	**267 mg**	**Capsule**	**12.7679**	**Days 1 to 7:** 1 capsule, TID (801 mg/d) **Days 8 to 14:** 2 capsules, TID (1,602 mg/d) **Day 15 onward:** 3 capsules, TID (2,403 mg/d)	**First year: 41,138.17** **Subsequent years: 41,942.55**

d = day; TID = three times per day.
[a] Manufacturer's submission — confidential price.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 5: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS PIRFENIDONE + BSC RELATIVE TO BSC?

Pirfenidone (plus BSC) vs. BSC	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					x	
Drug treatment costs alone					x	
Clinical outcomes	x					
QoL		x				
Incremental CE ratio or net benefit calculation	$78,024 per QALY $63,114 per LY					

BSC = best supportive care; CE = cost-effectiveness; LY = life-year; NA = not available; QoL = quality of life; vs = versus.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 6: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?	X		
Comments (Reviewer to provide comments if checking "no")			
Was the material included (content) sufficient?	X		
Comments (Reviewer to provide comments if checking "poor")			
Was the submission well organized and was information easy to locate?	X		
Comments (Reviewer to provide comments if checking "poor")			

TABLE 7: AUTHOR INFORMATION

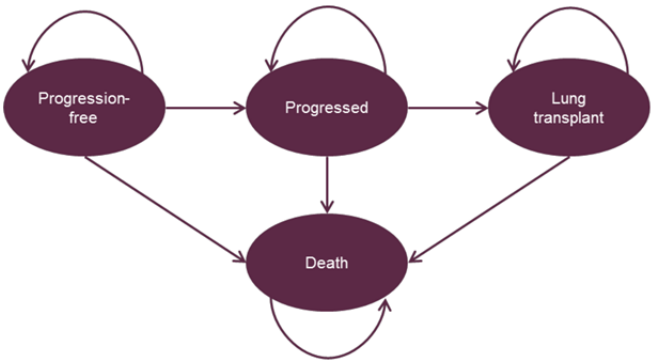
Authors	Affiliation		
Not stated	WG Consulting Healthcare Ltd.		
	Yes	**No**	**Uncertain**
Authors signed a letter indicating agreement with entire document		X	
Authors had independent control over the methods and right to publish analysis			X

APPENDIX 4: REVIEWER WORKSHEETS

1. Manufacturer's Model Structure

The manufacturer's model is a cohort-based, partitioned survival model that includes the health states of progression-free (initial health state), progressed, lung transplant, and death (Figure 1). Transition to the progressed health states is operationalized using the criteria used in the ASCEND trial (≥ 10% absolute decline in per cent predicted forced vital capacity (FVC), ≥ 50 m decline in 6MWT distance). Patients could only enter the lung transplantation state if their age was < 70 and if they were in the progressed health state. Transition to death could occur from any health state. Death is an absorbing state and could be entered into from any of the other states.

FIGURE 1: HEALTH STATES IN MANUFACTURER'S MODEL



Source: Manufacturer's Pharmacoeconomic Submission.

One thousand patients in each treatment strategy enter the model, all in the progression-free state. The proportion that transition to death from any of the states is calculated first. Surviving patients have a probability of remaining in the progression-free state; patients in the progressed state either remain in that state, transition to lung transplant, or transition to death. Patient cannot transition from the progressed state to the progression-free state. Each health state is assigned a cost and a utility.

Model validation was conducted by the manufacturer. In addition to technical validity, internal validity was assessed by comparing model-predicted outcomes with outcomes from the primary data sources. Note that for available randomized controlled trials (RCTs), this is limited to outcomes at 52 weeks and 72 weeks. Model-predicted survival, progression-free survival (PFS), and medication discontinuation was similar to the primary studies, indicating internal validity. Note that model-predicted outcomes after this time frame cannot be assessed for validity using RCT data.

2. Data Sources

TABLE 8: DATA SOURCES

Data Input	Description of Data Source	Comment
Overall survival — pirfenidone	Obtained from ASCEND, CAPACITY-1 and CAPACITY-2 and the RECAP extension studies by observing survival in pirfenidone-treated patients for up to 7 years of follow-up. Parametric survival analysis was conducted to predict long-term survival.	Uncertainty in true long-term survival with pirfenidone. Small number of patients in the latter stages of the extension trial.
Overall survival — BSC	Data from placebo groups of the ASCEND, CAPACITY-1, and CAPACITY-2 trials with 2 years of follow-up were considered, but were felt to be inadequate. Therefore, data from a longitudinal study (Strand 2014) were used. Parametric survival curves were fitted using this data.	Incremental survival was not based on RCT data, although the model-predicted survival similar to survival based on RCT data. Long-term survival was estimated.
PFS	The common definition of progression (ASCEND) was applied to pooled ASCEND/CAPACITY data and extrapolated beyond the study period using parametric survival analysis for both pirfenidone and placebo groups.	Data from 2-year RCT which was extrapolated over a patient lifetime.
Lung transplant	Occurs in patients < 70 years of age who are in the "progressed" health state, with a probability based on local sources, and similar regardless of treatment.	Reasonable assumption.
Utilities	Mapping of SGRQ to EQ-5D based on an external dataset using generalized mixed models; average SGRQ scores were generated from the CAPACITY studies.	Reasonable approach, but uncertainties exist in true utility-based QoL.
Resource use		
AEs (Indicate which specific AEs were considered in the model)	AEs not explicitly included in the model, but included as part of costs.	
Pirfenidone discontinuation	A survival curve for continuing on pirfenidone therapy was fitted, accounting for discontinuation due to AEs, patient's or sponsor's decision (proportion due to each not provided; patients were censored for death and transplantation). Approximately 60% have discontinued by 5 years and 85% by 10 years.	High discontinuation rate with continuing efficacy lack face validity. Biased in favour of pirfenidone (cost and efficacy).
Costs		
Drug	Use based on mean daily dose/pills per day in CAPACITY/ ASCEND. Cost per pill obtained from manufacturer.	
Disease management	Testing, oxygen, and liver function tests costs obtained from Ontario. Increased cost in progressed vs. progression-free ($333 vs. $258).	
AEs	Down titration to address photosensitivity accounted for in mean number of pills per day. Probability of hospitalizations for pirfenidone and BSC obtained from ASCEND/CAPACITY for SAE (similar between 2 groups). However, it is assumed that average LoS is twice as long in the BSC group (from CAPACITY).	It has not been established that LoS is truly different statistically; further it lacks face validity, given no difference in hospitalization rate.

Data Input	Description of Data Source	Comment
Lung transplant	Resource use based on expert opinion; workup costs estimated to be $20,000 (but only 1 out of 5 of patients will be transplanted); one-off transplantation costs are estimated to be $196,395. There are also ongoing costs of monitoring and immunosuppression in subsequent years.	Reasonable, but if fewer patients are in the progressed state, the implication is that the costs of workup and transplant will be less for pirfenidone-treated patients.
EoL costs	Higher for IPF-related deaths vs. non–IPF-related deaths based on EoL costs.	The data used to inform cost of IPF-related death are not specific; there is no evidence that costs differ.

AE = adverse event; EoL = end of life; EQ-5D = European Quality of Life Scale-5 Dimensions; IPF = idiopathic pulmonary fibrosis; LoS = length of stay; PFS = progression-free state; SGRQ = QoL = quality of life; St. George's Respiratory Questionnaire; RCT = randomized controlled trial; vs = versus.

3. Manufacturer's Key Assumptions

TABLE 9: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Manufacturer Justification/CDR Comment
Model structure	
IPF can be captured by the following health states: progression-free, progressed, lung transplant, and death.	While it is recognized that disease progression varies from patient to patient, the literature has found that declines in FVC ≥ 10% and 6MWT ≥ 50 m are both prognostic markers for disease progression, lower QoL, and increased mortality in the ensuing years. Therefore, it was important that the model structure capture such events. Upon consultation with clinicians, it was decided to adopt a heath state structure similar to that adopted by Loveman et al.[9] Reasonable assumption.
The costs and consequences of experiencing a progression are considered permanent (e.g., patients may not transition back to a progression-free state).	Aligned with published modelling in IPF and clinical evidence linking this decline to a permanent increase in the risk of mortality and a decrease in QoL. Reasonable assumption.
Only patients in the progressed disease state can undergo lung transplant.	Aligned with published modelling in IPF and clinical practice whereby patients typically have severe IPF and are aged < 70 years when receiving a lung transplant. Most patients with severe IPF will have had a progressive event. Reasonable assumption.
Clinical effectiveness	
Extrapolation of the Strand registry using parametric survival analysis was assumed to represent long-term survival with BSC.	The Strand registry enrolled a similar population to that of ASCEND/CAPACITY when considering the baseline characteristics of the clinical studies and registry. It was noted that the Strand registry may even have included a cohort of patients with less-severe disease when considering mean DL_{CO} alone. Of all registries evaluated, the Kaplan-Meier plot for the placebo groups of ASCEND/CAPACITY were closest to the Kaplan-Meier plot of the Strand registry. Survival outcomes up to 72 weeks were similar between ASCEND/CAPACITY and the Strand registry. Finally, it was noted that some patients in the Strand registry may have been misdiagnosed with IPF (based on the long tail of the Kaplan-Meier). Thus, using the Strand registry to represent BSC may be conservative in terms of estimating incremental outcomes compared with pirfenidone. While validity was established against RCT data over the short term (52 weeks), there was significant uncertainty about long-term mortality.

Assumption	Manufacturer Justification/CDR Comment
The probabilities of transitioning to the lung transplant state and subsequent mortality were assumed to occur only in patients < 70 years, and to remain constant over time.	While it is anticipated that time since diagnosis has an impact on the probability of a lung transplant, without data to inform this, the simplifying assumption of constant risk of transition over time was made. Reasonable assumption.
The proportion of IPF-related deaths was assumed to remain constant over time.	Without data capturing mortality outcomes beyond the duration of the ASCEND/CAPACITY studies, there was no evidence to suggest the proportion may change. Reasonable assumption.
Cost inputs	
Pulmonary rehabilitation costs are excluded from disease management and lung transplant costs.	A clinician indicated that due to funding limitations, patients typically receive 2 or 3 sessions of pulmonary rehabilitation only following transition to progressed disease. Since this is once in a patients' lifetime and occurs equally between pirfenidone and BSC, its inclusion would have no bearing on incremental costs. Although funding for pulmonary rehabilitation is available when a patient is on the waiting list for a lung transplant, it is challenging to identify the duration of rehabilitation treatment and there is a chance of double counting with EoL costs. Consequently, pulmonary rehabilitation was not included within disease management resource use. Reasonable assumption.
AEs not resulting in hospitalizations were assumed to have negligible costs.	AEs not resulting in hospitalization do not result in additional visits to the doctor or specialist, and are manageable with habit changes or down-titration of the dosage of pirfenidone, all of which are at zero cost. Reasonable assumption.
Lung transplant follow-up costs for cycle 2 onwards were assumed equal.	This simplification is likely a conservative assumption, since follow-up costs reduce as time increases. The average cost was calculated as costs borne from Month 3 to 2 years, with equal weight assumed. Reasonable assumption. Transplant-related costs have minimal impact on results.
EoL cost due to IPF is based on the cost accumulated by patients with organ failure. EoL cost due to causes other than IPF is an average of the cost accumulated by patients with frailty, sudden death, terminal illness, organ failure, and other causes.	This utilizes the best available data found in the public domain for increased costs in the last period of life for Canadian patients. Likely to apply to all patients; it is unclear whether this applies only to IPF-related causes of death.
QoL inputs	
Utility values used in mapping exercise were measured using the EQ-5D in UK patients and valued using the UK weights.	Due to the lack of data available for Canadian IPF patients, QoL data recorded for UK patients and valued using the UK algorithm were used to approximate QoL in Canadian IPF patients. Reasonable assumption.
Lung transplant utility assumed equal to progression-free disease.	There are sparse data and literature to inform lung transplant utilities in IPF. However, it would appear that a successful lung transplant may result in a similar if not improved QoL to progression-free disease, based on a study by Groen et al.[10]
Cycle length and time horizon	
The model adopts quarterly cycles and a lifetime time horizon of up to 33 years.	The model cycle was aligned with ASCEND and CAPACITY data collection points. A lifetime time horizon was used in line with CADTH guidelines. This time horizon assumed that patients could live until the age of 100 years, after which all patients were assumed to die. Reasonable assumption.
Patient transition between health states was assumed to occur midway through each 3-month cycle.	Recommended practice for calculating state occupancy over time, thereby avoiding overestimation/underestimation of state occupancy at each time point.[11] Reasonable assumption.

BSC = best supportive care; CDR = CADTH Common Drug Review; DL_{CO} = diffusing capacity for carbon monoxide; EoL = end of life; EQ-5D = European Quality of Life Scale-5 Dimensions; FVC = forced vital capacity; IPF = idiopathic pulmonary fibrosis; QoL = quality of life.
Source: Manufacturer's pharmacoeconomic submission, Table 25.

4. Manufacturer's Results

Treatment with pirfenidone results in incremental costs of $129,471 compared with BSC, primarily driven by drug acquisition costs. Pirfenidone results in an additional 1.7 QALYs (2.1 LY), with an ICUR of $78,024 (Table 2, Table 10).

TABLE 10: DISAGGREGATED REFERENCE CASE RESULTS

Cost category / Health state ($)	Progression-free	Progressed	Lung transplant	Death	Total
Pirfenidone					
Treatment	69,499	58,125	-	-	127,625
Disease management	2,891	5,145	-	-	8,035
Adverse events	6,190	11,070	-	-	17,260
Total costs	78,580	74,340	9,014	23,763	185,697
QALYs	2.368	3.210	0.130	0.000	5.709
Life years	-	-	-	-	7.056
Best supportive care					
Treatment	0	0	-	-	0
Disease management	1,779	3,492	-	-	5,272
Adverse events	6,572	9,687	-	-	16,259
Total costs	8,352	13,179	7,378	27,317	56,226
QALYs	1.670	2.272	0.107	0.000	4.049
Life years	-	-	-	-	5.004
Incremental					
Treatment	69,499	58,125	-	-	127,625
Disease management	1,111	1,652	-	-	2,764
Adverse events	-382	1,383	-	-	1,001
Total costs	70,229	61,161	1,636	-3,554	129,471
QALYs	0.698	0.938	0.024	0.000	1.659
Life years	-	-	-	-	2.051

Source: Manufacturer's pharmacoeconomic submission.

5. CDR Reanalysis

TABLE 11: CDR REANALYSIS

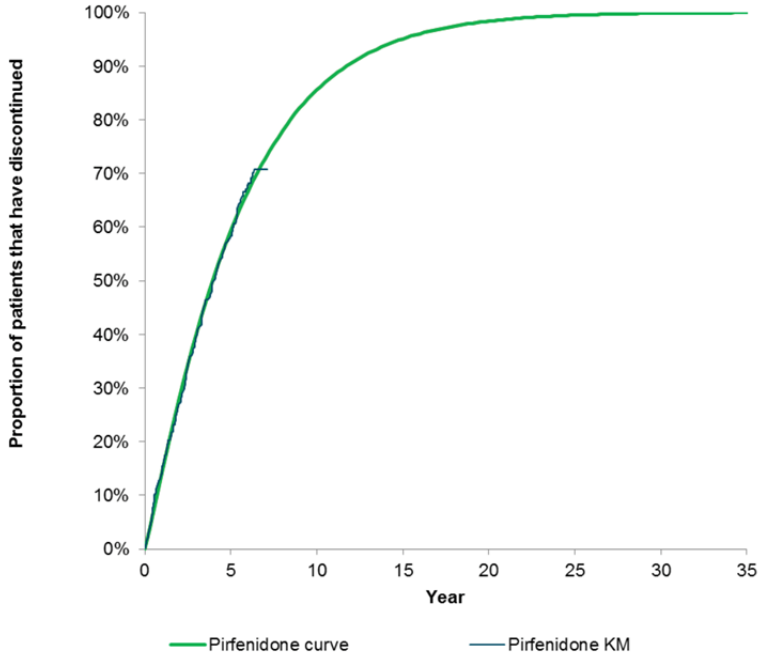
	Issue	Value	ICUR (Pirfenidone vs. BSC) ($)
1	There is no evidence of differential rates of hospitalization (not statistically significant, but baseline rates where probability is lower for pirfenidone was used in model) or LoS (twice the LoS for BSC, but no evidence that this is statistically significant; further, this lacks face validity).	Identical probability of hospitalization and LoS. Probability = 5.22%, LoS 8.48 days for both groups.	79,543
2	In the reference case, the number of IPF-related deaths were assumed to be greater than non–IPF-related deaths (which may favour pirfenidone), but data to support this are lacking.	Same EoL costs.	78,478
3	Use "piecemeal" parametric modelling. The modelled survival curve for mortality for BSC in the reference case differs from the observed (RCT) survival. The piecemeal modelling uses data directly from the RCT, then uses estimates after 2 years.	Trial followed by Strand registry survival for BSC.	82,488
4	The model fits a curve to estimate discontinuation due to AEs, patient's or sponsor's decision, with approximately 60% discontinuation at 5 years and 85% at 10 years. The CDR clinical expert suggested that most of the discontinuation would occur in the first 1 to 2 years, and would then flatten (note RCT data indicates discontinuation of 14% at 52 weeks and 20% at 72 weeks). It also lacks face validity in that overall efficacy in the cohort would be the same at 1 to 2 years (most people still on the drug) as at > 5 years, when most people are no longer taking the drug. (It is not clearly described that efficacy would be attenuated if patients discontinued the drug; the survival curves suggest there is no change in modelled relative efficacy). The clinical study report indicates discontinuation due to AEs is 14.4% in the trial.	25% discontinuation at 2 years with no further discontinuation. 20% discontinuation at 1.5 years with no further discontinuation. 15% discontinuation at 1 year with no further discontinuation.	124,672 130,792 137,230
5	While there is no difference in the probability of transplant, given modelled progression there will be more patients in the "progressed" state; therefore, the total number of patients undergoing transplant workup and transplantation (both are costly) will be greater in the BSC group. To determine the impact of this assumption, the cost of transplant workup, transplantation, and transplant management costs are set to zero.	Zero transplantation costs.	77,038

	Issue	Value	ICUR (Pirfenidone vs. BSC) ($)
6	In order to determine the distribution of costs and benefits, shorter time horizons were examined.	Time horizon: 2 years	462,211 (QALY gain = 0.116; LY gain = 0.133)
		5 years	188,271 (QALY gain = 0.509; LY gain = 0.610)
		10 years	106,941 (QALY gain = 1.122; LY gain = 1.376)
7	Plausible CDR reference case.	• Identical probability of hospitalization and LoS. • Same EoL costs. • Survival for BSC: trial followed by Strand registry. • Discontinuation rate plateaus at 25% at 2 years.	136,744

AE = adverse event; BSC = best supportive care; CDR = Common Drug Review; EoL = end of life; ICUR = incremental cost-utility ratio; IPF = idiopathic pulmonary fibrosis; LoS = length of stay; LY = life-year; QALY = quality-adjusted life-year; RCT = randomized controlled trial; vs = versus.

APPENDIX 5: FIGURES FROM MANUFACTURER'S SUBMISSION

FIGURE 2: PROBABILITY OF PIRFENIDONE DISCONTINUATION OVER TIME



*NB: discontinuation was due to adverse events, patient's decision, sponsor's decision, lost to follow up and other reasons

FIGURE 3: OVERALL SURVIVAL CURVE FIT (BASE CASE USING WEIBULL PARAMETRIC APPROACH)

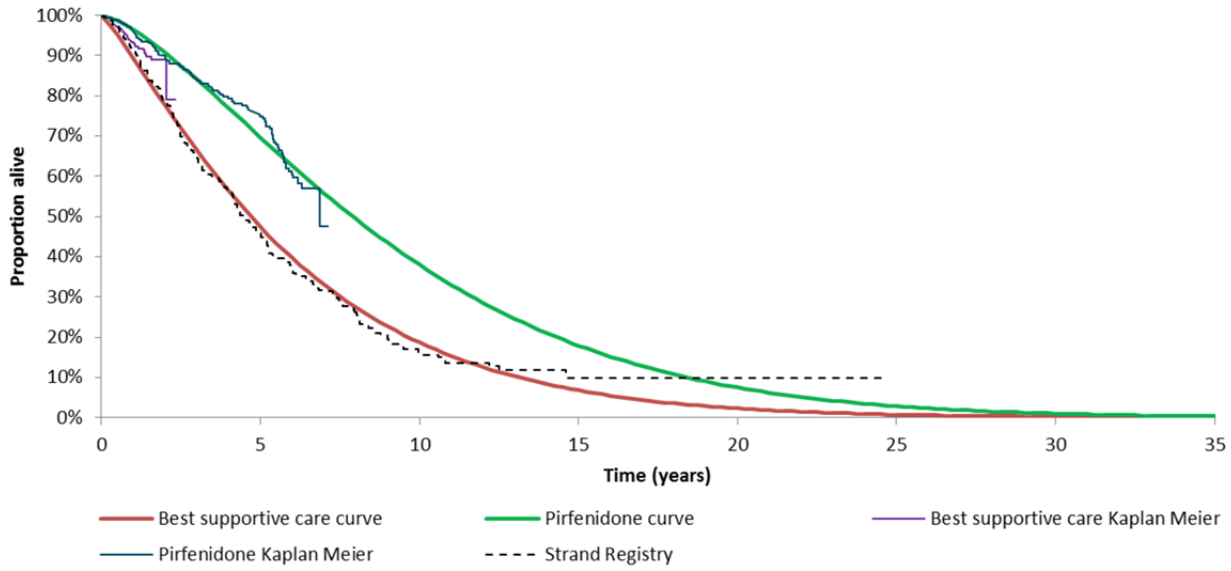
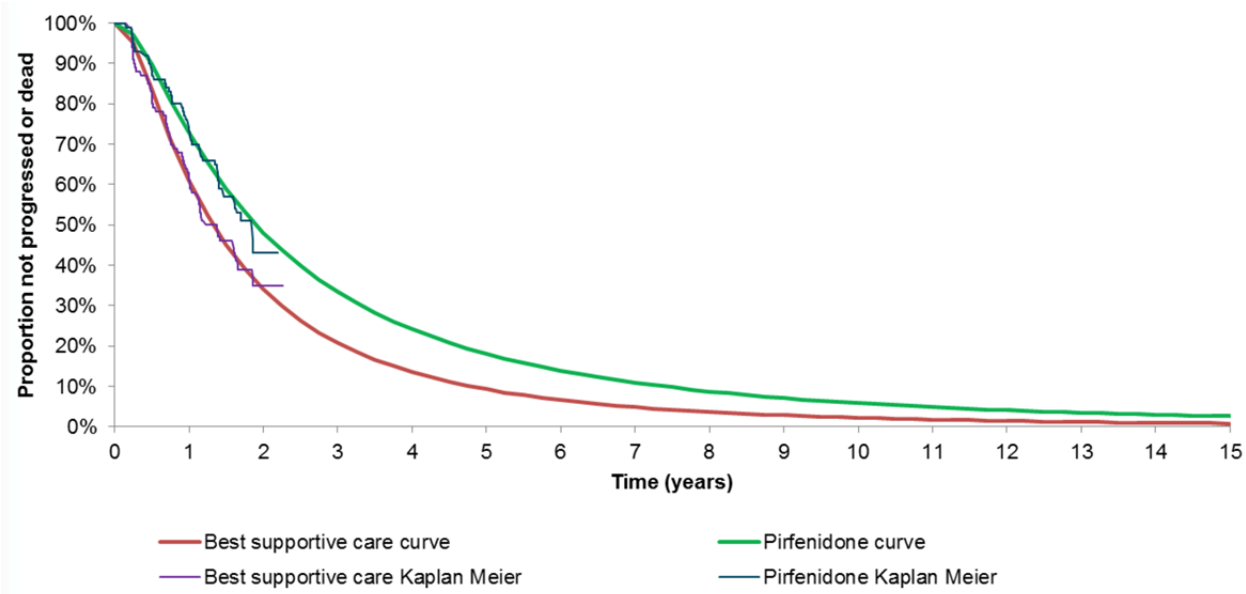


FIGURE 4: FIT OF PFS CURVES AGAINST BEST SUPPORTIVE CARE KAPLAN-MEIER DATA



PFS = progression-free survival.

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