CDEC FINAL RECOMMENDATION

PIRFENIDONE RESUBMISSION
(Esbriet — Hoffmann-La Roche Limited)
Indication: Idiopathic Pulmonary Fibrosis

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that pirfenidone be listed for the treatment of adults with mild to moderate idiopathic pulmonary fibrosis (IPF), if the following clinical criteria and conditions are met:

Criteria:
- Mild to moderate IPF, defined as forced vital capacity (FVC) greater than or equal to 50% of predicted
- Stable disease, defined as FVC not decreased by ≥ 10% during the previous 12 months
- Treatment discontinued if FVC declines by ≥ 10% within any 12-month period while receiving therapy

Conditions:
- Patient is under the care of a specialist with experience in the diagnosis and management of patients with IPF
- Substantial price reduction

Reason for the Recommendation:
1. A phase 3, randomized controlled trial (RCT) (ASCEND; N = 555) demonstrated that treatment with pirfenidone resulted in clinically significant improvements in per cent predicted FVC compared with placebo (mean difference 4.8% [95% confidence interval (CI) 2.4% to 7.2%]) at 52 weeks.
2. A pre-specified meta-analysis of three RCTs (CAPACITY-1, CAPACITY-2, and ASCEND) demonstrated a reduction in all-cause mortality (hazard ratio [HR] 0.52; 95% CI, 0.31 to 0.87) and IPF-related death (HR 0.42 [95% CI, 0.22 to 0.81]) with pirfenidone compared with placebo at 52 weeks.
3. Based on the CADTH Common Drug Review's (CDR) estimated incremental cost-utility ratio (ICUR) of $137,000 per quality-adjusted life-year (QALY) for pirfenidone versus best supportive care (BSC), CDEC concluded that pirfenidone is not a cost-effective treatment option at the submitted price ($12.77 per capsule or $115.00 per day).

Of Note:
All other causes of restrictive lung disease (e.g., collagen vascular disorders or hypersensitivity pneumonitis) should be excluded before initiating treatment for mild to moderate IPF.

Background:
Pirfenidone is an orally administered pyridine that suppresses pulmonary inflammation and excess collagen disposition through the inhibition of collagen synthesis induced by transforming growth factor and inhibiting the tumour necrosis factor. Pirfenidone has a Health Canada indication for the treatment of mild to moderate IPF in adults. Pirfenidone is available in 267 mg capsules and it is titrated over 14 days to a recommended dose of 2,403 mg/day.

Application History:
Pirfenidone was previously reviewed for the treatment of IPF by CDEC and received a recommendation of "do not list" (see *CDEC Final Recommendation* — April 18, 2013). The reason for the recommendation was as follows:

- The results of two placebo-controlled RCTs (CAPACITY-1 and CAPACITY-2) were inconsistent with respect to the statistical significance of improvements in the rate of decline of the per cent predicted FVC and the six-minute walk test (6MWT) with pirfenidone. In addition, there was insufficient evidence to determine if pirfenidone provides clinical benefit for mortality or quality of life.

The original CDR report included two RCTs of patients with mild to moderate IPF. CAPACITY-2 (N = 435) and CAPACITY-1 (N = 344) were 72-week, double-blind, multi-centre trials with similar protocols. In CAPACITY-1, patients were randomized (1:1) to pirfenidone 2,403 mg/day or placebo. Patients in CAPACITY-2 were randomized (2:2:1) to pirfenidone 2,403 mg/day, pirfenidone 1,197 mg/day, or placebo. The primary analysis of CAPACITY-2 compared the 2,403 mg/day dose with placebo. CDEC considered the following outcomes during its deliberations: all-cause mortality, IPF-related mortality, progression-free survival, World Health Organization–Quality of Life Questionnaire (WHO-QOL), St. George's Hospital Respiratory Questionnaire (SGRQ), FVC, acute IPF exacerbation, 6MWT, and adverse events.

In CAPACITY-1 and CAPACITY-2, there were no statistically significant differences between pirfenidone and placebo for all-cause mortality, IPF-related mortality, time to worsening of IPF, respiratory-related hospitalizations, dyspnea, need for supplemental oxygen, SGRQ, and WHO-QOL. Where statistical significance was demonstrated, it was generally inconsistent between CAPACITY-1 and CAPACITY-2. Specifically, progression-free survival and FVC were only significant in CAPACITY-2 and the 6MWT distance was only significant in CAPACITY-1. Exploratory pooled analyses suggested that pirfenidone was superior to placebo for IPF-related mortality, progression-free survival, FVC, and six-minute walking distance.

This resubmission is based on the new clinical information provided in the ASCEND trial.

Summary of CDEC Considerations:
CDEC considered the following information prepared by CDR:

- an updated systematic review of pirfenidone RCTs

- the final CDR clinical and pharmacoeconomic review reports from the initial pirfenidone application.
- a critique of the manufacturer's pharmacoeconomic evaluation
- a summary of the following additional clinical information provided by the manufacturer — a meta-analysis of the pirfenidone RCTs and an open-label extension study of the two CAPACITY trials (RECAP; N = 603)
- patient group-submitted information about outcomes and issues important to patients.

Patient Input Information

The following is a summary of key information provided by one patient group that responded to the CDR call for patient input:

- Patients with IPF experience breathlessness, fatigue, loss of energy, reduced physical activity, and a chronic cough. IPF affects one's ability to stay physically active, to work, and to participate in social activities. The stress arising from the diagnosis and the prognosis greatly affects patients' quality of life and mental well-being.
- There are limitations to currently available therapies for IPF, and patients are willing to tolerate side effects for a treatment that would slow the progression of IPF and improve their quality of life.
- Patients recognize that pirfenidone is not a cure, but hope that it will slow disease progression and the worsening of their most debilitating symptoms, and help them live longer.

Clinical Trials

The updated CDR systematic review included one additional RCT of patients with mild to moderate IPF. ASCEND (N = 555) was a 52-week, double-blind, multi-centre trial. In this trial, patients were randomized to pirfenidone 2,403 mg/day or placebo.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. CDEC discussed the following outcomes:

- All-cause mortality and IPF-related mortality.
- Acute IPF exacerbation — defined as events with all of the following criteria occurring within a four-week period: worsening oxygen saturation; clinically significant worsening of dyspnea; new, superimposed ground-glass opacities on high resolution computed tomography in at least one lobe; and all other causes had been ruled out.
- Percentage of predicted FVC — volume of air that can be forcibly exhaled from the lungs after taking in the deepest breath possible.
- 6MWT — the distance a patient can walk on a flat surface during the course of six minutes.
- Progression-free survival — defined as the time to the first occurrence of any of the following: death, confirmed ≥ 10% absolute decline from baseline in per cent predicted FVC, or confirmed ≥ 50 m decline from baseline in 6MWT distance.
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

The primary outcome in ASCEND was the change in percentage of predicted FVC from baseline to week 52.

Efficacy

- There was no statistically significant difference in all-cause mortality in ASCEND (HR 0.55; 95% CI, 0.26 to 1.15; *P* = 0.10) or IPF-related mortality in ASCEND (HR 0.44; 95% CI, 0.18 to 1.04; *P* = 0.23).
- The pirfenidone group had statistically significantly lower frequency of acute exacerbations (8.6%) than the placebo group (14.4%) (*P* = 0.034).
- There was a statistically significant improvement in the rate of decline in per cent predicted FVC with pirfenidone compared with placebo in ASCEND (mean difference 4.8%; 95% CI, 2.4% to 7.2%). This change is comparable to the minimal clinically important difference (MCID) for this outcome, which is estimated to be between 2% and 6%.
- The mean decline in the 6MWT distance was lower for patients treated with pirfenidone than placebo (mean difference 26.7 m; 95% CI, 8.3 m to 44.9 m).
- Those treated with pirfenidone demonstrated a statistically significant increase in progression-free survival than with placebo in ASCEND (HR 0.57%; 95% CI, 0.43 to 0.77).
- Meta-analyses of ASCEND, CAPACITY-1, and CAPACITY-2 demonstrated a statistically significant reduction in the risk of all-cause mortality at 52 weeks (HR 0.52; 95% CI, 0.31 to 0.87; calculated by the manufacturer) and IPF-related mortality at 52 weeks (HR 0.42; 95% CI, 0.22 to 0.81; calculated by CDR).
- Subgroup analyses suggested similar efficacy in FVC change in three ranges of baseline FVC (>80%, 65% to 80%, and <65%).

Harms (Safety and Tolerability)

- The proportion of patients who experienced at least one serious adverse event was lower in the pirfenidone group (19.8%) than in the placebo group (24.9%).
- The proportion of patients who reported at least one adverse event was similar for pirfenidone (99.6%) and placebo (98.2%). The most commonly reported adverse events in the pirfenidone group were nausea, rash, dyspnea, anorexia, and gastro-esophageal reflex.
- The proportion of patients who withdrew from the trial as a result of adverse events was higher in the pirfenidone group (14.4%) compared with the placebo group (10.8%).

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing pirfenidone with BSC (defined as symptom relief, pulmonary rehabilitation, management of comorbidities, and end of life care, including oxygen therapy), in adults 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; survival for BSC was obtained from a published observational study. Mathematical models were used to estimate long-term relative efficacy (survival and progression of disease). Quality of life was assigned by mapping the health state to SGRQ and subsequently to an EQ-5D score. The manufacturer reported that treatment with pirfenidone resulted in an incremental cost per QALY of $78,024 compared with BSC.

CDR noted the following key limitations with the manufacturer's pharmacoeconomic submission:

- The manufacturer assumed continued discontinuation of pirfenidone over time, such that at four years 50% of patients were no longer on pirfenidone, which increased to 85% at 10 years. 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. If

discontinuation remains constant at 25% after two years, the incremental cost per QALY for pirfenidone compared with BSC increases to $124,672.
- The manufacturer used data from an observational trial to inform BSC mortality, and RCTs with extension trial data to inform survival on pirfenidone. Model predicted versus RCT predicted survival are similar (over the duration of the RCT), but fitted survival curves are used to estimate long-term survival for both groups. It is not 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 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, with RCT data, to inform the first two years of survival; assumption of no difference in risk or duration of hospitalization; and, similar end of life costs, leading to an incremental cost per QALY for pirfenidone compared with BSC of $79,758. Where clinical uncertainty was further assessed through the exploration around the discontinuation rates, the ICUR increased from $136,744 (discontinuation rate with pirfenidone flattens to 25% at 2 years) to $143,569 (discontinuation rate of 15% at 1.5 years). If relative efficacy attenuates over time, the ICUR will be greater.

The submitted price for pirfenidone is $12.77 per capsule. At the recommended dose of 2,403 mg per day (3 x 267 mg capsules three times daily), the daily cost is $115.

Other Discussion Points:
CDEC noted the following:
- Pirfenidone has a Health Canada indication for the treatment of mild to moderate IPF in adults; however, CDEC noted that there is the potential for broader use outside the scope of the approved indication (e.g., severe IPF).
- CDEC noted that the listing criteria for pirfenidone currently used by many of the CDR-participating drug plans requires both of the following as part of the diagnosis for mild to moderate IPF: FVC between 50% to 80% predicted and the per cent of diffusing capacity for carbon monoxide (DLCO) between 30% and 90% predicted. CDEC considered these criteria and noted that challenges with the application and analysis of the DLCO limit its utility in evaluating the severity of IPF.
- At the recommended dose, patients are required to take three capsules, three times daily (total of nine capsules daily). Although, this is a large pill burden, CDEC noted that patients with mild to moderate IPF are likely to be compliant given the severity of this condition.

Research Gaps:
CDEC noted that there is insufficient evidence regarding the longer term efficacy and safety of pirfenidone.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets:

February 18, 2015: Two CDEC members were unable to attend the meeting.
April 8, 2015: None

Conflicts of Interest:

February 18, 2015: None
April 8, 2015: None

About This Document:

CDEC provides formulary listing recommendations or advice to CDR-participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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