FINAL CDEC RECOMMENDATION

PIRFENIDONE
(Esbriet – InterMune International AG)
Indication: Idiopathic Pulmonary Fibrosis

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that pirfenidone not be listed.

Reason for the Recommendation:
The results of two placebo-controlled, randomized controlled trials (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 forced vital lung capacity (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.

Of Note:
Given the uncertain clinical benefit of pirfenidone and concerns with the transparency of the economic model, CDEC was unable to adequately assess the cost-effectiveness of pirfenidone, but noted that the Common Drug Review (CDR) best estimates of incremental cost per quality-adjusted life-year (QALY) exceed the estimate of $143,617 reported by the manufacturer.

Background:
Pirfenidone has a Health Canada indication for the treatment of mild-to-moderate idiopathic pulmonary fibrosis (IPF) in adults. 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 the inhibition of tumour necrosis factor. Pirfenidone is available in 267 mg capsules, and it is titrated over 14 days to a recommended dose of 2,403 mg/day.

Summary of CDEC Considerations:
CDEC considered the following information prepared by CDR: a systematic review of RCTs of pirfenidone, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients. The manufacturer submitted a confidential price for pirfenidone.

Patient Input Information

Five provincial / national patient groups responded to the CDR call for patient input. Patient groups stated that:

- Patients with IPF experience debilitating breathlessness, chronic dry cough, and fatigue.
- IPF affects one's ability to work, socialize, travel, and participate in leisure activities.
- Improvement in quality of life, slowed disease progression, and a reduced need for oxygen therapy are outcomes of importance.
- There are limitations to currently available therapies for IPF.
- Patients would be willing to tolerate side effects as long as they were reversible and not worse than the disease itself.
- They recognize that pirfenidone is not a cure, but they hope it will effectively slow the progression of their disease.

Clinical Trials

The systematic review included two RCTs of patients with mild-to-moderate IPF. CAPACITY-2 (N = 435) and CAPACITY-1 (N = 344) were 72-week, double-blind, multicentre trials with similar protocols. In the CAPACITY-1 trial, 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.

Outcomes

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

- All-cause mortality, IPF-related mortality, progression-free survival.
- World Health Organization – Quality of Life Questionnaire (WHO-QoL) – where score ranges from 4 to 20, with lower scores indicating poorer quality of life.
- St. George's Hospital Respiratory Questionnaire (SGRQ) – a 50-item questionnaire that measures distress due to respiratory symptoms, mobility and physical activity, and the psychosocial impact of the disease. Scores range from 0 to 100, with higher scores indicating poorer quality of life.
- Percentage predicted FVC – the volume of air which can be forcibly exhaled from the lungs after taking the deepest breath possible.
- Acute IPF exacerbation – defined as events with all of the following criteria occurring within a four-week period: worsening of partial pressure of oxygen in the blood (PaO_2); clinically significant worsening of dyspnea; new, superimposed ground-glass opacities on high resolution computed tomography in at least one lobe; and all other causes of IPF had been ruled out.
- 6MWT – the distance a patient can walk on a flat surface in six minutes.
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

The primary outcome in both CAPACITY-1 and CAPACITY-2 was the change in the percentage of predicted FVC from baseline to week 72.

Results

Based on the Health Canada recommended dosing, CDEC focused its discussion on the results reported for the 2,403 mg/day dose of pirfenidone.

Efficacy

- There was no statistically significant difference in all-cause mortality in CAPACITY-1 (hazard ratio [HR] 0.95; 95% CI: 0.48 to 1.87) or CAPACITY-2 (HR 0.61; 95% CI: 0.28 to 1.29).
- There was no statistically significant difference in IPF-related mortality in either of the individual trials; however, an exploratory pooled analysis of IPF-related mortality suggested that pirfenidone was associated with a statistically significantly higher probability of survival compared with placebo (pooled HR 0.48; 95% CI: 0.24 to 0.95).
- Pirfenidone demonstrated a statistically significant increase in progression-free survival compared with placebo in CAPACITY-2 (HR 0.64; 95% CI: 0.44 to 0.95); however, there was no significant difference in CAPACITY-1 (HR 0.84; 95% CI: 0.58 to 1.22). A pooled analysis demonstrated an increase in progression-free survival with pirfenidone versus placebo (pooled HR 0.74; 95% CI: 0.57 to 0.96).
- There was a statistically significant improvement in the rate of decline in the per cent predicted FVC with pirfenidone compared with placebo in CAPACITY-2 (mean difference [MD] 4.4%; 95% CI: 0.7 to 9.1), but there was no statistically significant difference in CAPACITY-1 (MD 0.6%; 95% CI: 3.5 to 4.7). A pooled analysis demonstrated a statistically significant improvement in the rate of decline in the per cent predicted FVC improvement with pirfenidone compared with placebo of 2.5% (P = 0.005).
- In both trials, the mean decline in the 6MWT distance was lower for patients treated with pirfenidone than placebo; however, the difference was only statistically significant in CAPACITY-1 (MD 31.8 m; 95% CI: 3.5 to 60.1). A pooled analysis demonstrated a statistically significant lower reduction in the test distance with pirfenidone compared with placebo (MD 23.7 m; 95% CI: 4.2 to 43.2).
- There were no statistically significant differences between pirfenidone and placebo in the SGRQ or WHO-QoL.
- There were no statistically significant differences between pirfenidone and placebo for time to worsening of IPF, respiratory-related hospitalizations, dyspnea, or the need for supplemental oxygen.

Harms (Safety and Tolerability)

- The proportion of patients who experienced at least one serious adverse event was similar between pirfenidone and placebo.
- The proportion of patients who reported at least one adverse event was similar for pirfenidone (97.4%) and placebo (97.7%). The most commonly reported adverse events in the pirfenidone group were nausea, rash, dyspnea, vomiting, and photosensitivity.
- The proportion of patients who withdrew from the trial as a result of adverse events was higher in the pirfenidone group (14.8%) compared with placebo (10.7%).

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis that compared pirfenidone with placebo in patients with mild-to-moderate IPF over a lifetime horizon (60 years). The analysis considered IPF and non–IPF-related mortality, frequency and duration of hospitalization, and quality of life. Patient age, gender, FVC, and 6MWT distance measurements at baseline were used to estimate mortality, hospitalization frequency, and quality of life. The FVC and 6MWT distance data from the trials (CAPACITY-1, CAPACITY-2, and GIPF-007) were used to predict IPF-related mortality, probability of hospitalization, and quality of life, independent of treatment

allocation using regression models. Utility values were estimated first using the SGRQ score using a regression equation based on 6MWT distance and FVC, and then the SGRQ score was mapped onto the EQ-5D score using data from a study of patients with chronic obstructive pulmonary disease. Resource use was determined from expert opinion. Canadian unit costs were extracted from the Ontario Schedule of Benefits, Ontario Home Oxygen Program, Alberta Health and Wellness, and literature. The manufacturer reported that pirfenidone compared with placebo is associated with an incremental cost-utility ratio (ICUR) of $143,617 per QALY.

CDR identified a number of limitations with the manufacturer's economic submission:

- Issues with the transparency of the manufacturer's economic model limited its ability to be used to explore effects on survival. The manufacturer assumed a mortality benefit through week 72 (despite the lack of statistical significance in the CAPACITY trials), with the benefits persisting beyond week 72. When attempting to account for this, the ICUR ranged from $233,888 (no mortality benefit after 72 weeks) to $699,457 (based on a CDR re-analysis using a HR of 0.92 for the first 72 weeks and no benefit beyond 72 weeks).
- The manufacturer adjusted the HR for IPF-related mortality to reflect an assumed improved mortality with pirfenidone (HR 0.53; 95% CI: 0.29 to 1.03), censored at week 72. If FVC and 6MWT predicted mortality is used (HR 0.92), the ICUR increases to $231,487 per QALY gained compared with placebo (CDR re-analysis).
- The duration of benefit of pirfenidone as well as disease progression with treatment are unknown; however, a substantial amount of clinical benefit occurs during a longer analysis time frame. If efficacy attenuates over time, the ICUR will be higher.

At the recommended dose (three 267 mg capsules three times daily), the daily cost of pirfenidone is *[confidential price removed at manufacturer's request]*.

Other Discussion Points:

CDEC noted the following:

- The cause of death was not adjudicated by an independent committee; therefore, decisive conclusions about IPF-related mortality could not be made from CAPACITY-1 and CAPACITY-2.
- 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.
- The manufacturer conducted a meta-analysis of the FVC data from CAPACITY-1 and CAPACITY-2; however, the pre-specified statistical analysis plan stated that if one of the trials did not meet the criteria for superiority versus placebo for the primary efficacy end point (i.e., change in FVC), then the pooled analysis should be regarded as exploratory.
- Although individual patients may benefit from treatment with pirfenidone, CDEC was unable to determine the clinical criteria that would accurately identify these patients in clinical practice.

CDEC Members:
Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

March 20, 2013 Meeting

Regrets:
One CDEC member could not attend the meeting.

Conflicts of Interest:
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 requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final 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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