

Committee to Evaluate Drugs (CED)

Recommendations and Reasons

Document Posted: May 2015

Pirfenidone

Product: Pirfenidone (Esbriet®)

Class of Drugs: anti-fibrotic / anti-inflammatory agent

Reason for Use: idiopathic pulmonary fibrosis (IPF)

Manufacturer: InterMune Canada Inc.

Date of Review: May 8, 2013

CED Recommendation

The CED recommended Esbriet® (pirfenidone) not be funded for the treatment of idiopathic pulmonary fibrosis (IPF). The CED found that the benefits of pirfenidone were not consistently demonstrated in the clinical trials submitted by the manufacturer. There is no conclusive evidence that pirfenidone reduces mortality or improves quality of life. The CED recognized that IPF is a serious and debilitating disease with limited treatment options and noted that more compelling evidence is required regarding the drug's efficacy and cost-effectiveness to substantiate a funding recommendation.

Executive Officer Decision*

Taking into consideration the CED's recommendation and based on an agreement with the manufacturer to help address the CED's concerns regarding the cost and use of pirfenidone in patients with IPF, the Executive Officer decided to fund pirfenidone through the Ontario Drug Benefit's (ODB) Exceptional Access Program for the treatment of IPF according to specific criteria.

Funding Status*

Funded through the ODB's Exceptional Access Program (EAP) according to specific criteria.

(EAP criteria can be found at: http://www.health.gov.on.ca/en/pro/programs/drugs/eap_criteria.aspx)

** This information is current as of the posting date of the document. For the most up-to-date information on Executive Officer decision and funding status, see: www.health.gov.on.ca/en/pro/programs/drugs/status_single_source_subm.aspx.*

Highlights of Recommendation:

- Pirfenidone is an oral medication used for the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF) in adults.
- The effectiveness of pirfenidone was inconsistent based on the results of two clinical trials (CAPACITY-1 and CAPACITY-2). A pooled analysis of the data showed statistically positive benefits on the percent predicted forced vital lung capacity (%FVC) and the six-minute walk test (6MWT). The improvements were noted to be small and the clinical importance of these changes was unclear.
- The two studies failed to show that pirfenidone improved a patient's quality of life or reduced mortality.
- There is no information available to suggest that pirfenidone delays IPF disease progression.
- At the recommended dose of three 267mg capsules three times daily, the annual cost of treatment is \$41,138 for the first year (including the initial treatment doses) and \$41,942 for subsequent years (\$114.91 daily). Pirfenidone is not considered cost-effective.
- Overall, the CED found that the benefits of pirfenidone were not consistently demonstrated in the clinical trials submitted by the manufacturer. There is no conclusive evidence that pirfenidone reduces mortality or improves quality of life. The CED recognized that IPF is a serious and debilitating disease with limited treatment options and noted that more compelling evidence is required regarding the drug's efficacy and cost-effectiveness to substantiate a funding recommendation.

Background:

Idiopathic pulmonary fibrosis (IPF) is a progressive, irreversible fibrotic lung disease of unknown cause with disease onset typically occurring after age 60. In Canada, the prevalence of all forms of pulmonary fibrosis is estimated to be 113.1/100,000, and approximately 5,000 Canadians die from IPF each year. Several non-drug therapies are recommended for IPF patients, including long-term oxygen therapy, mechanical ventilation and pulmonary rehabilitation. Lung transplantation is also recommended for IPF patients; however, there are no clear data to guide precise timing and eligibility of transplantation.

There are few drug options for IPF. N-acetylcysteine (NAC), azathioprine and prednisone were used previously as combination therapy but the results from a clinical trial, that was stopped, showed increased hospitalizations and death in patients receiving this treatment. Various other treatments (e.g., immunosuppressants, endothelin receptor agonists) are used on a case-by-case basis in the absence of good evidence. Acute exacerbations (i.e., episodic worsening) are often treated with steroids, although there are no good data to support this treatment.

Detailed Discussions:

- For this funding evaluation, the CED took into consideration:
 - Findings from the Common Drug Review and the recommendation of the Canadian Drug Expert Committee.
 - Information in the manufacturer's submission.

- Submissions from two patient groups.
- The CED evaluated two randomized, placebo-controlled trials, CAPACITY-1 and CAPACITY-2.
- While there was a statistically significant improvement in the change in percentage of predicted forced vital capacity (%FVC) with pirfenidone compared to placebo in CAPACITY-2, the difference with %FVC in CAPACITY-1 was not statistically significant. In contrast, there was a statistically significant difference seen in the mean decline in the six-minute walk test (6MWT) in CAPACITY-1, while there was no statistically significant difference with 6MWT in CAPACITY-2. There were concerns regarding the conflicting results between these two trials.
- A pooled analysis of both CAPACITY trials indicated that pirfenidone was associated with a statistically significant improvement in both %FVC (i.e., 2.5%) and 6MWT (i.e., 23.7m) when compared to placebo. Although these values were considered statistically significant, the overall clinical significance of the changes was questioned as the absolute differences were noted to be small.
- Results of two quality of life (QOL) measures failed to show a statistically significant difference between pirfenidone and placebo, suggesting that pirfenidone did not improve QOL.
- Both trials failed to demonstrate statistically significant differences between pirfenidone and placebo for time to worsening of IPF (i.e., disease progression), respiratory-related hospitalizations, dyspnea, gas transfer, and the need for supplemental oxygen.
- There was no conclusive evidence that pirfenidone reduced mortality. The studies did not show differential rates of all-cause mortality between pirfenidone- and placebo-treated patients. Although a pooled analysis of IPF-related mortality suggested that pirfenidone was associated with a statistically significant higher probability of survival compared to placebo, IPF-related mortality was not significantly lower in either of the individual trials.
- CAPACITY-1 and CAPACITY-2 enrolled only patients with mild to moderate IPF. There is a lack of evidence to support the use of pirfenidone in patients with severe IPF.
- Pirfenidone was fairly well tolerated by patients in the studies. Pirfenidone is a CYP1A2 substrate and the potential exists for drug interactions. The clinical significance of these interactions is not clear.
- It was noted that an ongoing trial of 500 patients assessing the efficacy and safety of pirfenidone in IPF (ASCEND trial) was underway and once complete, may provide further information on the role of pirfenidone in treating IPF. (*Addendum: Results of the ASCEND trial are now published and have been submitted to the Common Drug Review for evaluation.*)
- At the recommended dose of pirfenidone (i.e., three capsules three times daily), the daily cost is \$114.91. The CED noted that the treatment costs are high while the clinical benefits are uncertain. The manufacturer's economic analysis had many limitations and was not able to show that pirfenidone is cost-effective.

- The CED reviewed two submissions from patient groups and recognized that IPF is a severe, progressive and debilitating disease with limited treatment options and that there is currently no other drug treatment specifically approved for this indication.
- The CED noted that although there may be a subgroup of patients that may derive benefit from pirfenidone treatment, those patients could not be identified based on currently available evidence.
- Overall, the CED found that the benefits of pirfenidone were not consistently demonstrated in the clinical trials submitted by the manufacturer. There is no conclusive evidence that pirfenidone reduces mortality or improves quality of life. The CED recognized that IPF is a serious and debilitating disease with limited treatment options and noted that more compelling evidence is required regarding the drug's efficacy and cost-effectiveness to substantiate a funding recommendation.

Committee to Evaluate Drugs (CED)

The Committee to Evaluate Drugs (CED) is comprised of practicing physicians, pharmacists, health economics experts, and patients. In conducting its review, the CED considers data contained in the drug manufacturer's submission, input provided by patient groups, findings from the national Common Drug Review and the pan-Canadian Oncology Drug Review, and other scientific information as necessary.

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