CDEC FINAL RECOMMENDATION

INDACATEROL MALEATE
(Onbrez – Novartis Pharmaceuticals Canada Inc.)
Indication: Chronic Obstructive Pulmonary Disease

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that indacaterol be listed in a similar manner to other long-acting beta2-agonists (LABAs) for the treatment of chronic obstructive pulmonary disease (COPD), at a dose not to exceed 75 mcg per day.

Reasons for the Recommendation:
1. In two, 12-week, double-blind randomized controlled trials (RCTs) of patients with moderate to severe COPD, compared with placebo, indacaterol 75 mcg daily was associated with statistically significant improvements in trough forced expiratory volume in one second (FEV_1).
2. At recommended doses, the daily cost of indacaterol (75 mcg once daily; *[confidential price removed at manufacturer's request]*) is less expensive than salmeterol (50 mcg twice daily; $1.88), but similar to formoterol (12 mcg to 24 mcg twice daily; $1.68 to $3.36).

Background:
Indacaterol has a Health Canada indication for long-term, once-daily, maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema. Indacaterol is a LABA, available as a hard gelatin capsule containing 75 mcg of micronized powder for inhalation. The Health Canada-approved dose is 75 mcg once daily.

Summary of CDEC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of double-blind RCTs of indacaterol, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Clinical Trials

The systematic review included four manufacturer-sponsored, double-blind, placebo-controlled, RCTs of patients with moderate to severe COPD. Two trials (B2354, n = 323; and B2355, n = 318) were identically designed, 12-week, phase 3, multicentre trials comparing indacaterol 75 mcg once daily with placebo. Two trials (B2335s and B2356) were two-week, dose-finding studies. None of the included trials were designed to compare indacaterol with other active treatments for COPD, although both two-week studies contained active treatment groups; formoterol or tiotropium (study B2335s) and salmeterol (study B2356). All four trials enrolled patients 40 years of age or older with moderate to severe COPD (FEV_1 of 30% to 80% of the predicted value).

In all four trials inhaled corticosteroids were allowed at pre-study doses and salbutamol was allowed for rescue therapy.

The percentage of patients withdrawing from the trials was higher for placebo groups compared with indacaterol in both B2354 and B2355; 19% versus 12% and 11% versus 7% respectively. In B2356, 2% of indacaterol and salmeterol groups and 3% in the placebo group withdrew. In B2335s, the percentages of patients withdrawing were 13%, 8%, 6%, and 4% in the placebo, indacaterol 75 mcg, tiotropium, and formoterol groups respectively.

The reviewed studies are limited by their short duration and the lack of comparisons between indacaterol 75 mcg and other active treatments. Further, none of the included trials were designed to assess the comparative efficacy of indacaterol in terms of COPD exacerbations, hospitalizations, or mortality. Finally no RCTs compared the efficacy and safety of indacaterol 75 mcg plus inhaled corticosteroids versus indacaterol alone.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: trough FEV_1, dyspnea, quality of life, COPD exacerbations, hospitalization, mortality, and serious adverse events.

Quality of life was measured using the St. George's 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 100 to 0, with higher scores indicating lower quality of life. The minimal clinically important difference for the SGRQ is considered to be four units.

Dyspnea was measured using the Transition Dyspnea Index (TDI). The TDI consists of three domains: functional impairment, magnitude of task, and magnitude of effort. Each domain is scored from –3 (major deterioration) to 3 (major improvement) and scores are summed such that total scores can range from –9 to 9; minus scores indicate deterioration, and a change of one unit is considered to be the minimal clinically important difference.

The primary outcome in all studies was the trough FEV_1 at end of treatment (12 weeks in B2354 and B2355, two weeks in B2335s and B2356).

Results

Efficacy or Effectiveness

- In studies B2354 and B2355, compared with placebo, trough FEV_1 at 12 weeks was statistically significantly greater for indacaterol; mean difference (MD): 0.12 L and 0.14 L respectively.
- Trough FEV_1 was statistically significantly greater for indacaterol 75 mcg groups compared with placebo at two weeks in both B2335s and B2356; MD: 0.15 L and 0.11 L respectively. Although neither B2335s nor B2356 were designed to compare indacaterol with other LABAs or tiotropium, changes from baseline in trough FEV_1 were similar for all active treatments.
- Indacaterol was associated with statistically significant and clinically important improvements in the TDI compared with placebo in B2354, but not in B2355.
- Neither of the two, 12-week trials reported a statistically significant between-treatment difference in the percentage of nights without awakenings. The percentage of days without daytime symptoms was statistically significantly higher for indacaterol compared with placebo in B2354, but not B2355. The percentage of days able to perform usual daily activities was statistically significantly higher for indacaterol compared with placebo in B2355, but not B2354.
- Compared with placebo, indacaterol was associated with statistically significant improvements in SGRQ scores in both B2354 and B2355; however, MDs did not exceed the minimal clinically important difference of four units; MD: –3.8 and –3.6 respectively.
- In both 12-week studies, compared with placebo, indacaterol resulted in statistically significantly larger reductions from baseline in the number of puffs of rescue medication per day: –1.16 and –0.66 in study B2354 and B2355 respectively. The percentage of 'days with no rescue medication use' was also statistically significantly higher in the indacaterol groups compared with the placebo in both B2354 and B2355.

Harms (Safety and Tolerability)

- The incidence of serious adverse events and withdrawal due to adverse events was similar between treatment groups in all trials, although numerical differences, where observed, favoured indacaterol.
- Adverse effects known to be associated with other LABAs such as tremor, nervousness, and palpitations did not appear to occur more frequently with indacaterol versus placebo.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing indacaterol with long-acting bronchodilators (tiotropium, salmeterol, and formoterol) for the treatment of patients with COPD based on the results of a network meta-analysis. At recommended doses, the daily cost of indacaterol (75 mcg once daily; *[confidential price removed at manufacturer's request]*) is less expensive than tiotropium (18 mcg once daily; $2.10) and salmeterol (50 mcg twice daily; $1.88), but similar to formoterol (12 mcg to 24 mcg twice daily; $1.68 to $3.36). The confidential price was used by the Committee in making the listing recommendation and the manufacturer requested that this information be kept confidential pursuant to the CDR Confidentiality Guidelines.

Patient Input Information:
The following is a summary of information provided by one patient group that responded to the CDR Call for Patient Input:

- Patient group input emphasized the progressive and debilitating nature of the condition and that patients living with COPD live ever more constricted and isolated lives, finding it increasingly hard to breathe, talk, work, and sleep.
- Patient group input suggests that COPD is often inadequately managed and that currently available treatments may be better used to help patients with COPD.
- Patients indicate there is a need for treatments that will slow the rate of decline in lung function. In addition, patients desire treatments that will improve breathing and day-to-day function, and thus quality of life.

Other Discussion Points:

- The Committee discussed that, in contrast to the European Medicines Agency, Health Canada and the US Food and Drug Administration did not approve indacaterol doses of 150 mcg or 300 mcg daily. The Committee noted that, based on the submitted price, indacaterol doses of 150 mcg or 300 mcg daily would result in costs approximately two- or four-fold higher than other available LABAs.
- The Committee discussed that the manufacturer-provided network meta-analysis suggests the efficacy of indacaterol 75 mcg is comparable to other LABAs and tiotropium. However, none of the available RCTs were appropriately designed for head-to-head comparisons.

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.

July 18, 2012 Meeting

Regrets:
None

Conflicts of Interest:
One CDEC member did not vote due to considerations of conflict of interest.

About this Document:
CDEC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC made its recommendation. 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 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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