CDEC FINAL RECOMMENDATION

GLYCOPYRRONIUM BROMIDE
(Seebri – Novartis Pharmaceuticals Canada Inc.)
Indication: Chronic Obstructive Pulmonary Disease

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that glycopyrronium bromide be listed for the treatment of chronic obstructive pulmonary disease (COPD) with the following condition:

- List in a manner similar to tiotropium.

Reasons for the Recommendation:

1. Two randomized controlled trials (RCTs) (GLOW-1 and GLOW-2) demonstrated statistically significant improvements in trough FEV1 with glycopyrronium compared with placebo. GLOW-1, GLOW-2, and a network meta-analysis suggested that glycopyrronium and tiotropium have similar efficacy for improving lung function in patients with COPD.

2. At recommended doses, the daily cost of glycopyrronium ($1.77 for 50 mcg) is less than the daily cost of tiotropium ($2.17 for 18 mcg).

Background:
Glycopyrronium bromide (glycopyrronium) is an inhaled long-acting muscarinic receptor antagonist with a Health Canada indication for the long-term maintenance bronchodilator treatment in patients with COPD, including chronic bronchitis and emphysema. Glycopyrronium is available as a 50 mcg powder in a hard capsule, the contents of which are inhaled through the Breezhaler device. The recommended dosage of glycopyrronium is 50 mcg once daily.

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

Patient Input Information

One patient group responded to the CDR call for patient input. The patient group stated the following:

- Since COPD is treated in a stepwise manner by layering treatments as the disease progresses, additional options are needed as the disease progresses and symptoms worsen.
- COPD exacerbations are associated with short-term and long-term consequences on health status and can lead to further exacerbations, decline in lung function, worsening quality of life, social withdrawal, depression and anxiety, and increased risk of hospitalization and mortality.

Clinical Trials

The systematic review included three RCTs: one 26-week, double-blind, placebo-controlled trial (GLOW-1, N = 822); one 52-week, double-blind placebo-controlled trial with an open-label tiotropium group (GLOW-2, N = 1,066); and one 52-week open-label trial comparing glycopyrronium with tiotropium (GLOW-4, N = 163). GLOW-2 and GLOW-4 were not designed to compare the efficacy of glycopyrronium against tiotropium. All of the included trials enrolled patients who were at least 40 years of age, had moderate or severe COPD, and had smoked at least 10 pack-years.

Outcomes

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

- All-cause mortality and hospitalizations.
- COPD exacerbations – defined as the worsening of two or more of dyspnea, sputum volume, and sputum purulence for at least two consecutive days, or worsening of any one major symptom together with any one of the following minor symptoms for at least two consecutive days: sore throat; colds (nasal discharge and/or nasal congestion); fever without other cause; increased cough; increased wheeze; and requiring treatment with systemic (oral or parenteral) corticosteroids and/or antibiotics.
- Trough FEV1 – defined as the mean of FEV1 measurements at 23 hours 15 minutes and 23 hours 45 minutes after the previous dose.
- The Transition Dyspnea Index (TDI) – score is based on three categories (functional impairment, magnitude of task, and magnitude of effort) each scored from –3 to 3, to give an overall score of –9 to 9. The minimum clinically important difference (MCID) for this outcome has been reported as an improvement of at least one unit.
- 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 MCID for the SGRQ is considered to be four units.
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

The primary outcome in GLOW-1 and GLOW-2 was trough FEV1 at 12 weeks, and adverse events in GLOW-4.

Results

Efficacy

- The rate of moderate or severe COPD exacerbations was significantly lower with glycopyrronium compared with placebo in GLOW-2 (rate ratio 0.66; 95% confidence interval [CI], 0.50 to 0.89); however, the difference in GLOW-1 was not statistically significant (rate ratio 0.72; 95% CI: 0.50 to 1.03). There was no statistically significant difference in the rate of moderate or severe COPD exacerbations between glycopyrronium and tiotropium in GLOW-2 (CDR-calculated rate ratio 0.82; 95% CI: 0.61 to 1.09); however, CDR calculated a lower rate with glycopyrronium compared with tiotropium in GLOW-4 (rate ratio 0.72; 95% CI: 0.45 to 0.95).
- Glycopyrronium was associated with a statistically significant increase in the time to first moderate or severe COPD exacerbation compared with placebo in GLOW-1 (hazard ratio [HR] = 0.69; 95% CI: 0.50 to 0.95) and GLOW-2 (HR 0.66; 95% CI: 0.52 to 0.85). There was no statistically significant difference between glycopyrronium and tiotropium in GLOW-2 (HR 1.09; 95% CI: 0.83 to 1.42).
- Glycopyrronium demonstrated statistically significant improvements in trough FEV1 at 12 weeks compared with placebo; mean differences (MD) were 0.108 L (95% CI: 0.079 to 0.137) and 0.097 L (95% CI: 0.065 to 0.130) in GLOW-1 and GLOW-2 respectively. There was no statistically significant difference in trough FEV1 between glycopyrronium and tiotropium in GLOW-2 (MD 0.019 L; 95% CI: –0.018, 0.057).
- Glycopyrronium was associated with a statistically significant improvement in TDI at 26 weeks compared with placebo in GLOW-1 (MD 1.04; 95% CI: 0.58 to 1.50) and GLOW-2 (MD 0.81; 95% CI: 0.30 to 1.32). There was no statistically significant difference in TDI between glycopyrronium and tiotropium in GLOW-2 (MD –0.13; 95% CI: –0.625 to 0.367).
- Glycopyrronium was associated with a statistically significant improvement in SGRQ compared with placebo, in GLOW-1 (MD –2.81; 95% CI: –4.70 to –0.93) and GLOW-2 (MD –3.32; 95% CI: –5.29 to –1.35). There was no statistically significant difference in SGRQ between glycopyrronium and tiotropium in either GLOW-2 (MD –0.48; 95% CI: –2.45 to 1.49) or GLOW-4 (CDR-calculated MD –3.04; 95% CI: –7.29 to 1.21).

Harms (Safety and Tolerability)

- The proportion of patients who experienced at least one adverse event was greater in the placebo group (65.2%) compared with the glycopyrronium group (57.6%) in GLOW-1. The proportion of patients with at least one adverse event was similar between placebo (76.5%), glycopyrronium (76.6%), and tiotropium (74.2%) in GLOW-2 and also between glycopyrronium (82.9%) and tiotropium (82.5%) in GLOW-4.
- The most common adverse events reported in the glycopyrronium groups were COPD exacerbations (20% to 36%) and nasopharyngitis (5% to 31%).
- The proportion of patients who experienced at least one serious adverse event was reported as follows: GLOW-1 (7.5% with glycopyrronium and 9.0% with placebo); GLOW-2 (12.4% with glycopyrronium, 15.0% with tiotropium, and 16.0% with placebo); and GLOW-4 (13.0% with glycopyrronium and 15.0% tiotropium).
- Withdrawals due to adverse events were slightly less frequent with glycopyrronium compared with placebo in GLOW-1 (5.8% versus 7.1%) and GLOW-2 (8.0% versus 11.6%), similar to tiotropium in GLOW-2 (8.0% versus 7.5%), and slightly lower than tiotropium in GLOW-4 (8.9% versus 12.5%).

Cost and Cost-Effectiveness
The manufacturer submitted a cost-minimization analysis that compared glycopyrronium with tiotropium for maintenance treatment in patients with COPD. Tiotropium was selected by the manufacturer as the most appropriate comparator as it is the only other long-acting anticholinergic drug reimbursed by public drug plans in Canada. The manufacturer assumed similar efficacy and tolerability between glycopyrronium and tiotropium based on the results of two post-hoc analyses of pooled data from the GLOW-1 and GLOW-2 studies and a network meta-analysis. Based on the recommended dose of 50 mcg daily, the daily cost of glycopyrronium ($1.77) is less than the daily cost of tiotropium ($2.17).

Other Discussion Points:
CDEC noted the following:

- There were no RCTs that were designed to compare glycopyrronium against tiotropium for the treatment of COPD; however, a network meta-analysis submitted by the manufacturer suggested that these two drugs have similar efficacy.
- The MCID for trough FEV1 is reported to be in the range of 0.1 L to 0.14 L. The difference between glycopyrronium and placebo was close to the lower end of the MCID range (0.108 L in GLOW-1 and 0.097 L in GLOW-2).

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.

April 17, 2013 Meeting

Regrets:
None

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 not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

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