CDEC FINAL RECOMMENDATION

TIOTROPIUM BROMIDE
(Spiriva Respimat — Boehringer Ingelheim Canada Ltd.)
Indication: Chronic Obstructive Pulmonary Disease

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that tiotropium bromide (Spiriva Respimat) be listed for the long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, and for the reduction of exacerbations, if the following condition is met:

Condition:
- List in a manner similar to Spiriva HandiHaler.

Reasons for the Recommendation:
1. One large, double-blind, randomized controlled trial (RCT) (TIOSPIR; N = 17,183) demonstrated that tiotropium 5 mcg once daily administered with the Respimat device (Tio R 5) was non-inferior to tiotropium 18 mcg once daily administered using the HandiHaler device (Tio H 18) for the risk of death. TIOSPIR also demonstrated that Tio R 5 was similar to Tio H 18 for reducing the risk of COPD exacerbations and for improving forced expiratory volume in one second (FEV_1). In addition, two smaller RCTs (studies 205.249 and 205.250) demonstrated that Tio R 5 was non-inferior to Tio H 18 for improving FEV_1.
2. Multiple RCTs demonstrated that Tio R 5 was statistically superior to placebo for reducing the risk of COPD exacerbations (three RCTs), improving FEV_1 (four RCTs), and improving health-related quality of life (two RCTs).
3. At the submitted price ($[redacted] per 4 mL cartridge), the daily cost of tiotropium administered with the Respimat device ($[redacted] per day) is less than the daily cost of tiotropium administered using the HandiHaler device ($2.17 per day) and [redacted] other long-acting anti-muscarinic (LAMA) products (i.e., aclidinium bromide and glycopyrronium bromide).

Background:
Spiriva Respimat is a new multi-dose, propellant-free, aqueous, soft mist aerosol delivery device that provides 2.5 mcg tiotropium per actuation. It is indicated as a long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema, and for the reduction of exacerbations. The recommended dose is two oral inhalations of 2.5 mcg tiotropium administered once daily using the Respimat device.

Summary of CDEC Considerations
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs and pivotal studies, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues that are important to individuals living with COPD.

Patient Input Information
The following is a summary of key information provided by four patient groups, consisting of patients and caregivers, that responded to the CDR call for patient input:

- COPD affects almost all aspects of daily living, including physical and leisure activities, as well as relationships with family and friends. The most common symptoms are fatigue and shortness of breath, followed by mucus, wheezing, frequent chest infections, and coughing. As patients lose the ability to perform daily activities, they may suffer from depression, hopelessness, frustration, a loss of self-worth, and have difficulty remaining employed.
- Patients reported a constant need for medications to treat their condition. As the condition worsens, they may require multiple medications and supplementary oxygen therapy. Current treatments provide some relief for fatigue, shortness of breath, cough, appetite loss, low energy, and inability to fight infection. However, these treatments can be limited by adverse effects such as palpitations, dry mouth, mouth sores, vision problems, urinary problems, and impaired mood.
- Patients indicated that new delivery devices with improved mechanisms to administer medication could improve compliance and significantly benefit those living with COPD.

Clinical Trials
The CDR systematic review included eight prospective double-blind RCTs: 205.249 (N = 131), 205.250 (N = 76), 205.251 (N = 361), 205.252 (N = 358), 205.254 (N = 983), 205.255 (N = 1,007), 205.372 (N = 3,991), and 205.452 (TIOSPIR; N = 17,183). All trials enrolled patients who were at least 40 years of age, had a diagnosis of moderate to severe COPD, and had a history of smoking (at least 10 pack-years).

- Study 205.452 (TIOSPIR) was a large, multi-centre, randomized, active-controlled, double-blind, double-dummy, parallel-group phase 3b trial conducted to evaluate the efficacy and safety of tiotropium 2.5 mcg once daily (Tio R 2.5) and Tio R 5 once daily compared with Tio H 18 mcg once daily. The trial had two co-primary end points: time to death (non-inferiority tested) and time to first COPD exacerbation (superiority tested).
- Studies 205.249 and 205.250 were 28-week, randomized, multi-centre, double-blind, double-dummy, placebo-controlled, crossover, non-inferiority and superiority, phase 3 and 2/3 trials, respectively. The trials compared four 4-week treatment periods of Tio R 5, Tio R 10, Tio H 18, and placebo.

- Studies 205.251 and 205.252 were 12-week, randomized, multi-centre, double-blind, double-dummy, parallel-group, non-inferiority and superiority trials. Patients were randomized to one of four treatment groups: Tio R 5, Tio R 10, ipratropium 36 mcg inhalation (Iprat 36), or placebo.
- Studies 205.254 and 205.255 were identical, 48-week, randomized, multi-centre, double-blind, placebo-controlled, parallel-group, phase 3 efficacy and safety studies. Patients were randomized to Tio R 5, Tio R 10, or placebo.
- Study 205.372 was a 48-week, randomized, double-blind, placebo-controlled, parallel-group phase 3b study to assess the long-term safety and superior efficacy of Tio R 5 once daily compared with placebo, in patients who continued to use their usual COPD therapy.

Data for the Tio R 2.5 once-daily and Tio R 10 once-daily treatment groups were not included in the CDR review or CDEC deliberations, as these are not approved doses for Spiriva Respimat in Canada.

Outcomes

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

- All-cause mortality.
- COPD exacerbations — defined as an increased symptom or new onset of two or more of the following for a duration of three days or more and requiring a change in treatment: shortness of breath or dyspnea, shallow, rapid breathing, sputum production, occurrence of purulent sputum, cough, wheezing, and chest tightness. A change in or requirement of treatment included the prescription of antibiotics and/or systemic corticosteroids and/or or a significant change of the prescribed respiratory medication.
- Trough FEV_1 — defined as the FEV_1 measured at the –10 minutes time point at the end of the dosing interval 24 hours post-drug administration on the last day of treatment. The minimal clinically important difference (MCID) is reported to be a change of 0.100 L to 0.140 L.
- St. George's Respiratory Questionnaire (SGRQ) — a self-administered 50-item instrument used to assess impaired health and perceived well-being in respiratory disease. The SGRQ is divided into three dimensions: symptoms, activity, and impacts. Total SGRQ scores range from 0 to 100, with higher values indicating lower health-related quality of life. The MCID has been reported to be an improvement of at least four units in the SGRQ total score.
- COPD symptoms scores — the severity of COPD symptoms (i.e., wheezing, shortness of breath, coughing, and tightness of chest) were scored based on the investigator's assessment of the patient's condition during the week just prior to the visit and evaluated prior to the conduct of pulmonary function tests using a scale ranging from 0 (none) to 3 (severe symptoms).
- Transition Dyspnea Index (TDI) focal score — an interviewer-administered instrument used to measure change from the baseline in the severity of breathlessness in patients. The scores evaluate ratings for three different categories: functional impairment, magnitude of task, and magnitude of effort. These domains are rated by seven grades, ranging from –3 (major deterioration) to +3 (major improvement). The ratings for each of the three categories are added to form a total TDI score ranging from –9 to +9. Lower TDI scores indicate more deterioration in the severity of dyspnea, and the MCID is considered to be one unit.

The primary efficacy outcome in studies 205.249, 205.250, 205.251, and 205.252 was trough FEV_1 response. In studies 205.254 and 205.255, there were four co-primary end points (trough FEV_1 response, SGRQ, TDI, and COPD exacerbations). There were two co-primary end points in TIOSPIR (time to death from any cause and time to first COPD exacerbation) and study 205.372 (trough FEV_1 response and time to first COPD exacerbation).

Efficacy

Longer-Term Trial (TIOSPIR)

- There were 423 deaths (7.4%) in the Tio R 5 group and 439 deaths (7.7%) in the Tio H 18 group over three years. The corresponding hazard ratio (HR) was 0.957 (95% confidence interval [CI], 0.837 to 1.094). The upper limit of the 95% CI for the HR was below the pre-specified non-inferiority margin of 1.25; therefore, Tio R 5 was non-inferior to Tio H 18 for all-cause mortality.
- Similar proportions of patients in the Tio R 5 and Tio H 18 groups experienced a COPD exacerbation (47.9% versus 48.9%), a moderate to severe COPD exacerbation (47.2% versus 48.0%), or were hospitalized due to a COPD exacerbation (14.5% versus 14.3%). The corresponding HRs for COPD exacerbations were:
  - Any COPD exacerbation: 0.978 (95% CI, 0.928 to 1.032); $P = 0.4194$
  - Moderate to severe COPD exacerbation: 0.983 (95% CI, 0.932 to 1.037); $P = 0.5377$
  - Hospitalization due to COPD exacerbation: 1.024 (95% CI, 0.929 to 1.128); $P = 0.6384$.
- In the subset of patients in the spirometry sub-study, Tio R 5 (n = 461) was non-inferior to Tio H 18 (n = 445) for trough FEV_1 response through 120 weeks. The adjusted mean treatment difference in FEV_1 was −0.010 L (95% CI, −0.038 to 0.018).

Shorter-Term Trials

- In a pooled analysis of studies 205.254 and 205.255, COPD exacerbations were reported for 37.2% of patients in the Tio R 5 group compared with 44.1% in the placebo group. The odds ratio (OR) for experiencing an exacerbation was 0.75 (95% CI, 0.60 to 0.93), favouring Tio R 5. Time to first exacerbation was also statistically significantly shorter in the placebo group compared with the Tio R 5 group (86 days versus 160 days; $P < 0.001$).
- Compared with placebo, statistically significantly fewer patients in the Tio R 5 group of study 205.372 experienced an exacerbation (35.3% versus 43.1%), a moderate to severe exacerbation (34.1% versus 27.7%), or were hospitalized due to an exacerbation (8.3% versus 10.1). The corresponding HRs for COPD exacerbations were:
  - Any COPD exacerbation: 0.693 (95% CI, 0.625 to 0.769); $P < 0.0001$
  - Moderate to severe exacerbation: 0.699 (95% CI, 0.622 to 0.786); $P < 0.0001$
  - Hospitalization due to exacerbation: 0.728 (95% CI, 0.589 to 0.901).
- For improving FEV_1, Tio R 5 was shown to be statistically superior to placebo in studies 205.249, 205.250, 205.251, and 205.252; non-inferior to Iprat 36 in study 205.251; superior to Iprat 36 in study 205.252; and non-inferior to Tio H 18 in studies 205.249 and 205.250. The mean differences (MDs) for these comparisons were:
  - Tio R 5 versus placebo: 0.109 L (95% CI, 0.036 to 0.181) in 205.251; 0.124 L (95% CI, 0.067 to 0.181) in 205.252; 0.116 L (95% CI, 0.083 to 0.149) in 205.249; and 0.126 L (95% CI, 0.086 to 0.166) in 205.250

  - Tio R 5 versus Tio H 18: 0.045 L (95% CI, 0.013 to 0.078) 205.249 and 0.001 L (95% CI, −0.039 to 0.041) in 205.250
  - Tio R 5 versus Iprat 36 mcg: 0.049 L (95% CI, −0.024 to 0.122) in 205.251 and 0.080 L (95% CI, 0.024 to 0.136) in 205.252.
- The Tio R 5 groups demonstrated statistically significant improvements in SGRQ compared with placebo in studies 205.254, 205.255, and 205.372. The MDs between Tio R 5 and placebo were:
  - Study 205.254: −3.269 (95% CI, −5.224 to −1.315)
  - Study 205.255: −3.713 (95% CI, −5.778 to −1.647)
  - Study 205.372: −2.9 (95% CI, −3.9 to −2.0).
- There were statistically significant improvements in TDI focal scores with Tio R 5 compared with placebo in studies 205.254 (MD 1.104 [95% CI, 0.667 to 1.540]) and 205.255 (MD 1.011 [95% CI, 0.531 to 1.490]).

Harms (Safety and Tolerability)

- The proportions of patients who experienced at least one adverse event were:
  - Four-week duration (studies 205.249 and 205.250): ranged from 28.6% to 54.7% with Tio R 5, 27.7% to 44.0% with Tio H 18, and 33.3% to 72.4% with placebo
  - 12-week duration (studies 205.251 and 205.252): ranged from 47.7% to 57.6% with Tio R 5, 55.1% to 64.0% with Iprat 36, and 49.5% to 68.9% with placebo
  - 48-week duration (studies 205.254, 205.255, and 205.372): ranged from 70.1% to 78.4% with Tio R 5 and 69.3% to 79.6% with placebo
  - TIOSPIR: 64.9% with Tio R 5 and 65.5% with Tio H 18.
- The proportions of patients who experienced at least one serious adverse event were:
  - Four-week duration (studies 205.249 and 205.250): ranged from 2.7% to 4.5% with Tio R 5, 1.3% to 3.6% with Tio H 18, and 2.6% to 4.6% with placebo
  - 12-week duration (studies 205.251 and 205.252): ranged from 2.2% to 2.3% with Tio R 5, 9.0% to 10.1% with Iprat 36, and 5.5% to 12.2% with placebo
  - 48-week duration (studies 205.254, 205.255, and 205.372): ranged from 13.6% to 18.6% with Tio R 5 and 16.8% to 17.1% with placebo
  - TIOSPIR: 32.4% with Tio R 5 and 32.4% with Tio H 18.
- The proportions of patients who withdrew as a result of adverse events were:
  - Four-week duration (studies 205.249 and 205.250): ranged from 1.3% to 2.7 with Tio R 5, 0% to 3.6% with Tio H 18, and 2.6% to 11.1% with placebo
  - 12-week duration (studies 205.251 and 205.252): ranged from 6.8% to 7.6% with Tio R 5, 10.1% to 12.4% with Iprat 36, and 5.5% to 12.2% with placebo
  - 48-week duration (studies 205.254, 205.255, and 205.372): ranged from 7.0% to 10.7% with Tio R 5 and 7.6% to 22.2% with placebo
  - TIOSPIR: 8.2% with Tio R 5 and 8.8% with Tio H 18.

Cost and Cost-Effectiveness

The manufacturer submitted a cost comparison of Tio R 5 once daily with Tio H 18 once daily, glycopyrronium bromide 50 mcg once daily, and aclidinium bromide 400 mcg twice daily. Similar pharmacokinetic exposure, efficacy, and safety between Tio R and Tio H were assumed on the basis of two 4-week crossover trials and the TIOSPIR trial. No evidence was submitted in the

pharmacoeconomic evaluation regarding clinical similarity between Tio R and aclidinium bromide or glycopyrronium bromide.

At the submitted price of $[redacted] per 60 dose inhaler ($[redacted] per day), Tio R is less expensive per patient annually than the current list price of Tio H ([redacted], without markup) and [redacted] compared with glycopyrronium bromide and aclidinium bromide. Tio R is also less expensive than available inhaled corticosteroid/long-acting beta-2 agonist (ICS/LABA) combination products, but more expensive than some individual LABA products. For patients requiring LAMA plus LABA therapy, currently available LAMA/LABA fixed dose combinations are less expensive than all possible combinations of Tio R plus a LABA.

Other Discussion Points:
CDEC noted the following:

- CDEC noted that there is a risk of dose escalation with pharmacotherapies for COPD, including tiotropium. There is no evidence to suggest that increasing the dosage of tiotropium to a level above the dose recommended in the product monograph (i.e., 5 mcg per day for tiotropium administered with the Respimat device) would be associated with increased clinical benefits for patients. In addition, increasing the dosage would result in greater costs for the CDR-participating drugs.

Research Gaps:
CDEC noted that there is an absence of evidence regarding the following:

- There are no direct comparisons of tiotropium administered with the Respimat device against other LAMAs approved for use in the treatment of COPD (e.g., aclidinium bromide, glycopyrronium bromide, and umeclidinium bromide).

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, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

June 17, 2015 CDEC Meeting

Regrets:
One CDEC member was unable to attend the meeting.

Conflicts of Interest:
One CDEC member did not participate in the vote.

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. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

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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