CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

TIOTROPIUM/OLODATEROL
(Inspiolto Respimat — Boehringer Ingelheim Canada Ltd.)
Indication: Chronic Obstructive Pulmonary Disease

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that tiotropium/olodaterol (TIO/OLO) 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 emphysema, if the following clinical criteria and condition are met:

Clinical Criteria:
- Moderate to severe COPD as defined by spirometry
- Inadequate response to a long-acting beta$_2$ agonist (LABA) or long-acting muscarinic antagonist (LAMA).

Condition:
- Drug plan costs for TIO/OLO should not exceed the drug plan costs for other LAMA/LABA combination products.

Reasons for the Recommendation:
1. Ten double-blind, randomized controlled trials (RCTs) demonstrated that treatment with TIO/OLO resulted in statistically significant improvements in lung function compared with its individual components as monotherapy, fluticasone propionate/salmeterol (FP/SAL), and placebo.
2. A manufacturer-submitted network meta-analysis (NMA) suggested that TIO/OLO has similar efficacy compared with other LAMA/LABA combination therapies for improving lung function, health-related quality of life, dyspnea, and COPD exacerbations.
3. At the submitted price ($2.10 per day), TIO/OLO is less costly than all other LAMA/LABA fixed-dose combination (FDC) products ($2.47 to $2.70 per day).

Background:
TIO/OLO is a LAMA/LABA FDC formulation indicated for long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema. It is available as a solution for oral inhalation using the Respimat

inhaler, with each actuation delivering TIO/OLO at a dose of 2.5/2.5 mcg. The recommended dose for TIO/OLO is 5/5 mcg once daily, given as two inhalations from the Respimat inhaler.

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 of TIO/OLO, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to patients living with COPD.

Patient Input Information
One patient group, the Ontario Lung Association, responded to the CDR call for patient input. Information was obtained from online surveys targeting COPD patients, caregivers, and physicians; phone interviews; and consultation with a certified respiratory educator. The following is a summary of information provided by the patient group:

- COPD is a progressive debilitating disease that impacts almost every aspect of normal daily life. The most frequent symptoms are shortness of breath, cough, fatigue, wheezing, and difficulty fighting infections. As shortness of breath and difficulty breathing develop, the resulting reduction in physical activity creates a downward spiral that affects patients' ability to talk, sleep, work, and socialize.
- The need for oxygen and medications is constant, and the inability to perform daily activities like housework, leisure activities, cooking, or shopping leave some people feeling frustrated, depressed, and hopeless.
- Patients reported that while current treatments provide some relief for COPD symptoms, a variety of significant adverse effects, which patients find problematic, are associated with these medications.
- Patients are looking for drugs that can improve lung function and quality of life, reduce exacerbations, delay disease progression, and improve survival.

Clinical Trials
The CDR systematic review included 10 phase 3, multi-centre, double-blind RCTs: TONADO 1 (N = 2,624), TONADO 2 (N = 2,539), OTEMTO 1 (N = 812), OTEMTO 2 (N = 809), Study 1237.22 (N = 122), VIVACITO (N = 219), MORACTO 1 (N = 295), MORACTO 2 (N = 291), TORRACTO (N = 404), and ENERGITO (N = 229). All studies enrolled patients who were at least 40 years of age with moderate to severe COPD. TONADO 1, TONADO 2, and VIVACITO also included patients with very severe COPD.

- TONADO 1 and TONADO 2 were 52-week, parallel-group RCTs comparing TIO/OLO 5/5 mcg with its individual components, TIO 5 mcg and OLO 5 mcg.
- OTEMTO 1 and OTEMTO 2 were 12-week, parallel-group RCTs comparing TIO/OLO 5/5 mcg with TIO 5 mcg and placebo.
- VIVACITO was a six-week, crossover study comparing TIO/OLO 5/5 mcg with its individual components and placebo.
- MORACTO 1 and MORACTO 2 were six-week, crossover exercise tolerance studies comparing TIO/OLO 5/5 mcg with its individual components and placebo.
- TORRACTO was a 12-week, parallel-group RCT comparing TIO/OLO 5/5 mcg with placebo.
- ENERGITO was a six-week, crossover study comparing TIO/OLO 5/5 mcg with fluticasone propionate/salmeterol (FP/SAL) 500/50 mcg and FP/SAL 250/50 mcg.

Outcomes

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

- All-cause and COPD-related mortality.
- COPD exacerbations — defined as a complex of lower respiratory events or symptoms (at least two of the following: shortness of breath, sputum production, purulent sputum, cough, wheezing, chest tightness) attributed to COPD, lasting at least three days, that required a change in treatment (use of antibiotics, systemic steroids, emergency treatment or hospitalization).
- Trough forced expiratory volume in one second (FEV_1) — defined as FEV_1 measured at the end of the dosing interval (24 h). In TONADO 1, TONADO 2, OTEMTO 1, OTEMTO 2, VIVACITO, and ENERGITO, this was calculated as the mean of two FEV_1 measurements performed at 23 h and 23 h 50 min after inhalation of study medication at the clinic visit on the previous day. In the exercise tolerance studies, trough FEV_1 was measured 30 minutes before dosing. The minimal clinically important difference (MCID) for FEV_1 is reported to be a change of 0.10 L to 0.14 L.
- Exercise endurance time (EET) — a measure of exercise endurance, assessed during constant work rate cycle ergometry (CWRCE) at the end of the treatment period. A maximal work capacity (Wcap) was determined for each patient at visit 1, defined as the maximum work rate achieved for at least 30 seconds during incremental cycle ergometry, where increasing loads are applied to the cycle as the patient pedals at a constant frequency until the patient stops from exhaustion.
- Transition Dyspnea Index (TDI) focal score — an interviewer-administered instrument used to measure change from 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 increasing severity of dyspnea, and the MCID is considered to be 1 unit.
- 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 4 units in SGRQ total score.
- Rescue salbutamol use — use of rescue medication was defined as the number of puffs used in the previous 24 h for as-needed relief of the symptoms of COPD.
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

Primary and co-primary end points in the included studies were: trough FEV_1 and FEV_1 area under the curve ($AUC_{0\text{-}3h}$) at 24 weeks (TONADO 1 and TONADO 2), trough FEV_1, FEV_1 $AUC_{0\text{-}3h}$, and SGRQ at 12 weeks (OTEMTO 1 and OTEMTO 2), FEV_1 $AUC_{0\text{-}24h}$ at six weeks (VIVACITO), FEV_1 $AUC_{0\text{-}12h}$ (ENERGITO), EET during CWRCE to symptom limitation at 75% Wcap (MORACTO 1, MORACTO 2, and TORRACTO), and inspiratory capacity at rest before CWRCE (MORACTO 1 and MORACTO 2).

Efficacy

- TIO/OLO 5/5 mcg demonstrated greater improvement in trough FEV_1 compared with TIO 5 mcg, OLO 5 mcg, and placebo. Mean differences between treatments were:
  - TIO/OLO 5/5 mcg versus TIO 5 mcg:
    - TONADO 1: 0.071 L (95% confidence interval [CI], 0.047 to 0.094); $P < 0.0001$
    - TONADO 2: 0.050 L (95% CI, 0.024 to 0.075); $P = 0.0001$
  - TIO/OLO 5/5 mcg versus OLO 5 mcg:
    - TONADO 1: 0.082 L (95% CI, 0.059 to 0.106); $P < 0.0001$
    - TONADO 2: 0.088 L (95% CI, 0.063 to 0.113); $P < 0.0001$
  - TIO/OLO 5/5 mcg versus placebo:
    - OTEMTO 1: 0.162 L (95% CI, 0.124 to 0.200); $P < 0.0001$
    - OTEMTO 2: 0.166 L (95% CI, 0.129 to 0.203); $P < 0.0001$.
- TIO/OLO 5/5 mcg demonstrated greater improvement in FEV_1 $AUC_{0\text{-}12h}$ and trough FEV_1 compared with FP/SAL 500/50 mcg and FP/SAL 250/50 mcg in ENERGITO. Mean differences for TIO/OLO versus FP/SAL 500/50 mcg and FP/SAL 250/50 mcg (respectively):
  - Trough FEV1: 0.058 L (95% CI, 0.034 to 0.082) and 0.047 L (95% CI, 0.022 to 0.071)
  - FEV_1 $AUC_{0\text{-}12h}$: 0.129 L (95% CI, 0.107 to 0.150) and 0.125 L (95% CI, 0.103 to 0.147)
- TIO/OLO 5/5 mcg demonstrated greater improvement in TDI focal score compared with TIO 5 mcg, OLO 5 mcg, and placebo; however, results across TONADO 1 and TONADO 2 were not consistent. Mean differences between treatments were:
  - TIO/OLO 5/5 mcg versus TIO 5 mcg:
    - [redacted]
  - TIO/OLO 5/5 mcg versus OLO 5 mcg:
    - [redacted]
  - TIO/OLO 5/5 mcg versus placebo:
    - OTEMTO 1: 2.052 (95% CI, 1.516 to 2.588); $P < 0.0001$
    - OTEMTO 2: 1.195 (95% CI, 0.665 to 1.725); $P < 0.0001$.
- TIO/OLO 5/5 mcg demonstrated greater improvement in SGRQ total score compared with TIO 5 mcg, OLO 5 mcg, and placebo; however, results across TONADO 1 and TONADO 2 were not consistent. Mean differences between treatments were:
  - TIO/OLO 5/5 mcg versus TIO 5 mcg:
    - [redacted]
  - TIO/OLO 5/5 mcg versus OLO 5 mcg:
    - [redacted]
  - TIO/OLO 5/5 mcg versus placebo:
    - OTEMTO 1: −4.894 (95% CI, −6.904 to −2.884); $P < 0.0001$
    - OTEMTO 2: −4.564 (95% CI, −6.499 to −2.629); $P < 0.0001$.
- TIO/OLO 5/5 mcg demonstrated greater improvement in EET during CWRCE compared with placebo (20.9% increase in MORACTO 1 [$P < 0.0001$]; 13.4% increase in MORACTO 2 [$P < 0.0001$]). In MORACTO 2, there was also a statistically significant increase in adjusted mean endurance time during CWRCE after six weeks for TIO/OLO 5/5 mcg compared with OLO 5 mcg (11.1% increase; $P = 0.0009$). In TORRACTO, there was a statistically

significant increase in endurance time during CWRCE after 12 weeks compared with placebo (13.8% increase; *P* = 0.0209).

Harms (Safety and Tolerability)

- Adverse events reported with TIO/OLO 5/5 mcg were generally similar with comparator treatments across studies. The most common adverse events across all trials were COPD exacerbations and nasopharyngitis. The proportions of patients who experienced at least one adverse event were:
  - [redacted]
  - 12 weeks: TIO/OLO 5/5 mcg, 41.5% to 44.8%; TIO 5 mcg, 42.7% to 45.8%; OLO 5 mcg, 40.4%; placebo, 41.6% to 51.5%
  - Six weeks: TIO/OLO 5/5 mcg, 33.9% to 38.5%; TIO 5 mcg, 34.1% to 44.2%; OLO 5 mcg, 37.7% to 40.1%; FP/SAL 500/50 mcg, 37.0%; FP/SAL 250/50 mcg, 29.7%; placebo, 40.1% to 46.4%.
- The proportions of patients who experienced at least one serious adverse event were:
  - [redacted]
  - Six weeks: TIO/OLO 5/5 mcg, 0.7% to 3.2%; TIO 5 mcg, 2.2% to [redacted]; OLO 5 mcg, [redacted] to 5.8%; FP/SAL 500/50 mcg, 4.1%; FP/SAL 250/50 mcg, 1.9%; placebo, [redacted] to 2.9%
  - 12 weeks: TIO/OLO 5/5 mcg, [redacted] to 4.9%; TIO 5 mcg, 3.0% to 5.9%; placebo, 2.0% to 5.4%.
- The proportions of patients who withdrew as a result of adverse events were:
  - [redacted]
  - Six weeks: TIO/OLO 5/5 mcg, 0.7% to 2.7%; TIO 5 mcg, [redacted]; OLO 5 mcg, [redacted] to 2.2%; FP/SAL 500/50 mcg, 1.4%; FP/SAL 250/50 mcg, 0.9%; placebo, [redacted]
  - 12 weeks: TIO/OLO 5/5 mcg, 0.5% to [redacted]; TIO 5 mcg, 1.5% to 3.4%; placebo, 5.0% to [redacted].

Cost and Cost-Effectiveness

The manufacturer submitted a cost comparison of TIO/OLO with other LAMA/LABA FDCs (indacaterol/glycopyrronium [IND/GLY], umeclidinium/vilanterol [UMEC/VI], aclidinium/formoterol [ACL/FM]) and ICS/LABA FDCs (budesonide/formoterol [BUD/FM], fluticasone furoate/vilanterol [FF/VI], FP/SAL) for the treatment of moderate to severe COPD over a one-year time frame. The manufacturer assumed similar efficacy and harms of TIO/OLO compared with other LAMA/LABA FDCs based on an NMA, and did not provide evidence to support the assumption compared with ICS/LABA FDCs.

CDR noted the following limitations with the manufacturer's pharmacoeconomic evaluation:

- Given the heterogeneity among the studies included in the NMA, there is uncertainty with respect to the comparative effectiveness of TIO/OLO with other LAMA/LABA FDCs.
- No evidence was provided to support the assumption of similar safety and efficacy of TIO/OLO with ICS/LABA FDCs other than FP/SAL.
- Comparison with various LABA or LAMA monotherapies, which are less costly than TIO/OLO, were not considered.

At recommended doses, TIO/OLO ($2.10 per day) is less costly than all other LAMA/LABA FDCs (IND/GLY: $2.68 per day, UME/VI: $2.70 per day, and ACL/FM: $2.47 per day). TIO/OLO is also less costly than separately administered LAMA + LABA monotherapies (range: $3.26 to $3.85), and ICS/LABA FDCs (BUD/FM: $2.80 per day, FF/VI: $4.00 per day, FP/SAL $3.25 to $4.61 per day).

Other Discussion Points:
CDEC noted the following:

- Olodaterol has been approved by Health Canada as a separate inhaler, but it is not currently marketed in Canada.
- The once-daily dosing of TIO/OLO may be advantageous for patients when compared with the twice-daily dosing regimens recommended for some other LAMA/LABA FDCs.

Research Gaps:
CDEC noted that there is insufficient evidence regarding the following:

- None of the included RCTs were designed or powered to assess treatment differences in COPD exacerbations.
- There are no direct comparisons of TIO/OLO versus other LAMA/LABA combination therapies.
- COPD is a chronic condition and all of the included RCTs were short-term studies.

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.

November 18, 2015 Meeting

Regrets:
None

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

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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