CDEC FINAL RECOMMENDATION

INDACATEROL/GLYCOPYRRONIUM
(Ultibro Breezhaler — Novartis Pharmaceuticals Canada Inc.)
Indication: Chronic Obstructive Pulmonary Disease

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that indacaterol maleate/glycopyrronium bromide (IND/GLY) be listed for the long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), if the following clinical criteria are met:

Clinical Criteria:
- Moderate to severe COPD, as defined by spirometry.
- Inadequate response to a long-acting bronchodilator (long-acting beta-2 agonist [LABA] or long-acting anticholinergic [LAAC]).

Reasons for the Recommendation:
1. Two randomized controlled trials (RCTs) demonstrated that IND/GLY was similar or statistically superior to a combination of formoterol and tiotropium (FOR + TIO) (QUANTIFY; N = 934) and a combination of fluticasone propionate/salmeterol (FP/SAL) (ILLUMINATE; N = 523) for improving forced expiratory volume in one second (FEV_1), quality of life, and dyspnea in patients with moderate to severe COPD.

2. At the submitted price ($2.68 per day), the IND/GLY combination product is less costly than the following comparators: IND + GLY used separately ($3.32 per day); FOR + TIO ($3.66 per day); FP/SAL ($3.25 to $4.61 per day); all currently available LABA + LAAC combinations (range: $3.26 to $4.04 per day); and all currently available inhaled corticosteroid (ICS)/LABA combination products (range: $2.76 to $4.61 per day).

Of Note:
CDEC noted that the listing status of LABA and LAAC products varies across the drug plans participating in the CADTH Common Drug Review (CDR).

Background:
Ultibro Breezhaler (IND/GLY) is a combination of a LABA and a long-acting muscarinic antagonist (LAMA), indicated for the long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and

emphysema. IND/GLY is available as inhalation powder hard capsules containing 110 mcg IND and 50 mcg GLY. The recommended dosage of IND/GLY is once-daily oral inhalation of one 110/50 mcg capsule using the Breezhaler device.

Summary of CDEC Considerations:
CDEC considered the following information prepared by CDR: a systematic review of RCTs of IND/GLY, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to individuals living with COPD.

Patient Input Information
The following is a summary of key information provided by two patient groups that responded to the CDR call for patient input:

- Individuals with COPD commonly experience difficulty breathing, as well as coughing, shortness of breath, fatigue, weakness, lack of appetite, and difficulty talking. Performing everyday tasks can be difficult and patients become limited in their ability to participate in social interactions, occupational activities, and leisure activities. The disease has a progressive debilitating course. People with COPD and their caregivers often experience anxiety and depression.
- Currently available treatments provide some symptom relief, but are limited by side effects such as palpitations, dry mouth, voice hoarseness, mouth sores, and visual and urinary problems. Exacerbations are often managed with prednisone, which can have dangerous side effects such as stomach upset and general swelling, and increases in the risk of osteoporosis and ophthalmic disease. There is also a concern that these medications lose effectiveness over time.
- Patient groups stated that treatments are needed to improve lung function and breathing, and that fast-acting treatments are particularly important to those patients who are employed.

Clinical Trials
Eight double-blind RCTs (QUANTIFY, SHINE, SPARK, ILLUMINATE, ENLIGHTEN, BEACON, BLAZE, and BRIGHT) and one open-label RCT (ARISE) met the inclusion criteria for the CDR systematic review. The dosage regimen for each active comparator used in the studies was as follows: IND/GLY (110/50 mcg once daily), IND alone (150 mcg once daily), GLY (50 mcg once daily), FOR (12 mcg twice daily), TIO (18 mcg once daily), and FP/SAL (500/50 mcg twice daily).

- QUANTIFY (N = 934) compared IND/GLY with a combination of FOR + TIO.
- SHINE (N = 2,135) compared IND/GLY with IND alone, GLY alone, and open-label TIO.
- SPARK (N = 2,224) compared IND/GLY with GLY alone, and open-label TIO.
- ILLUMINATE (N = 523) compared IND/GLY with FP/SAL.
- ENLIGHTEN (N = 339) compared IND/GLY with placebo.
- BEACON (N = 193) compared IND/GLY with a combination of IND and GLY administered separately.
- BLAZE (N = 247) and BRIGHT (N = 85) were crossover studies comparing IND/GLY, TIO, and placebo.
- ARISE (N = 160) compared IND/GLY with TIO.

All studies included patients with moderate to severe COPD, with the exception of SPARK, which included patients with severe to very severe COPD.

Outcomes

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

- COPD exacerbation — defined as a worsening of the following two or more major symptoms for at least two consecutive days: dyspnea, sputum volume, or sputum purulence; or a worsening of any one major symptom together with an increase in 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 coughing, increased wheezing; and requiring treatment with corticosteroids and/or antibiotic, emergency room visit, or hospitalization. Exacerbations were considered moderate if treatment with systemic corticosteroids and/or antibiotics was required and severe if hospitalization was required.
- St. George's Respiratory Questionnaire (SGRQ) — a 40-item questionnaire that measures distress due to respiratory symptoms, mobility and physical activity, and the psychosocial impact of the disease. A 4-point change is considered to be the minimal clinically important difference (MCID) for this instrument.
- Baseline Dyspnea Index — domains for functional impairment, magnitude of task, and magnitude of effort are rated from 0 (severe) to 4 (unimpaired) and the rates are summed for the baseline focal score, ranging from 0 to 12. Lower scores indicate greater severity of dyspnea.
- Transition Dyspnea Index (TDI) — domains for functional impairment, magnitude of task, and magnitude of effort are rated from –3 (major deterioration) to 3 (major improvement), and the rates are summed for the transition focal score, ranging from –9 to 9. Negative scores indicate worsening of dyspnea.
- Trough FEV_1 — assessed using the average of two pre-dose FEV_1 measurements. A change of 0.1 L is considered the MCID for trough FEV_1.
- FEV_1 area under the curve (AUC) (0 h to 12 h) — assessed using the standardized area under the curve from 0 h to 12 h post dose for FEV_1.
- Serious adverse events, total adverse events, withdrawals due to adverse events.

Primary end points of the included studies were as follows: SGRQ-C (QUANTIFY), rate of moderate to severe exacerbations (SPARK), FEV_1 AUC (0 h to 12 h) (ILLUMINATE), trough FEV_1 (SHINE and BEACON), safety and tolerability (ARISE and ENLIGHTEN), patient-reported dyspnea (BRIGHT), and exercise tolerance (BLAZE).

Efficacy

LAMA/LABA-Controlled Trial (QUANTIFY)

- There was a statistically significant difference in FEV_1 favouring IND/GLY compared with FOR + TIO, with a least squares mean difference [LS MD] of 0.07 L (95% confidence interval [CI], 0.04 to 0.10); $P < 0.001$).
- IND/GLY was non-inferior to TIO + FOR for change from baseline in total SGRQ-C scores. The LS MD between groups of –0.69 (95% CI, –2.31 to 0.92) in the full analysis set and –0.77 (95% CI, –2.48 to 0.93) in the per-protocol set met the criteria for non-inferiority, as the upper boundary of the CI was lower than the predefined margin for non-inferiority of 4 points.
- There was no statistically significant difference between IND/GLY (13%) and TIO + FOR (15%) for the proportion of patients who experienced a moderate to severe exacerbation.

- There was no statistically significant difference between IND/GLY and TIO + FOR in dyspnea scores after 26 weeks.

ICS/LABA-Controlled Trial (ILLUMINATE)

- IND/GLY was statistically superior to FP/SAL for the FEV_1 AUC (0 h to 12 h) with an LS MD of 0.14 L (95% CI, 0.10 to 0.18); $P < 0.001$.
- There were statistically significantly greater (improved) dyspnea scores with IND/GLY compared with FP/SAL (LS MD of 0.76 (95% CI, 0.26 to 1.26), $P = 0.003$).
- There was no statistically significant difference between IND/GLY and FP/SAL in SGRQ-C total scores or symptom scores.

Placebo-Controlled Trial (ENLIGHTEN)

- There was a statistically and clinically significant improvement in trough FEV_1 for IND/GLY versus placebo (LS MD of 0.19 L [95% CI, 0.13 to 0.25], $P < 0.001$).
- IND/GLY improved symptom scores versus placebo (LS MD of –0.57 [95% CI, –1.01 to –0.13], $P = 0.011$).

LAMA and Placebo–Controlled Trials (BLAZE and BRIGHT)

- After six weeks in BLAZE, there was a statistically and clinically significant improvement in FEV_1 AUC (five minutes to four hours) for IND/GLY versus placebo (LS MD of 0.33 L [95% CI, 0.31 to 0.36], $P < 0.001$) and versus TIO (0.11 L [95% CI, 0.08 to 0.13], $P < 0.001$). After three weeks in BRIGHT, there was a statistically significant improvement in trough FEV_1 for IND/GLY versus placebo (LS MD of 0.20 L [95% CI, 0.15 to 0.26], $P < 0.001$) and versus TIO (LS MD 0.10 L [95% CI, 0.05 to 0.15], $P < 0.001$).
- In BLAZE, there was a statistically significant improvement in TDI focal scores for IND/GLY versus placebo (LS MD of 1.37 [95% CI, 0.95 to 1.79], $P < 0.001$) and versus TIO (LS MD of 0.49 [95% CI, 0.07 to 0.91], $P = 0.021$). In BRIGHT, there was no statistically significant difference in change in dyspnea scores between IND/GLY and placebo or TIO.
- In BRIGHT, there was a statistically significant increase in exercise endurance for IND/GLY versus placebo (LS MD of 59.5 seconds [95% CI, 17.7 to 101.3], $P = 0.006$). There was no statistically significant difference in exercise endurance between IND/GLY and TIO.
- In BLAZE, there was a statistically significant improvement in symptom scores with IND/GLY compared with placebo (LS MD of –0.72 [95% CI, –0.94 to –0.49], $P < 0.001$) and no statistically significant difference between IND/GLY and TIO.

Component, LAMA, and Placebo–Controlled Trials (SHINE, SPARK)

- In SHINE, IND/GLY demonstrated superiority for trough FEV_1 over IND, GLY, TIO, and placebo. In SPARK, trough FEV_1 was also statistically significantly improved for IND/GLY versus TIO and GLY (all $P < 0.001$). LS MDs were reported as follows:
  - IND/GLY versus TIO: 0.07 L (95% CI, 0.06 to 0.09) in SPARK and 0.08 L (95% CI, 0.05 to 0.10) in SHINE.
  - IND/GLY versus GLY: 0.09 L (95% CI, 0.06 to 0.11) in SHINE and 0.08 L (95% CI, 0.07 to 0.10) in SPARK.
  - IND/GLY versus IND: 0.07 L (95% CI, 0.05 to 0.10) in SHINE.
  - IND/GLY versus placebo: 0.21 L (95% CI, 0.17 to 0.24) in SHINE.
- IND/GLY demonstrated statistically significant improvements over TIO for the SGRQ-C total score in SHINE (LS MD, –2.13 [95% CI, –3.72 to –0.54], $P = 0.009$) and in SPARK (LS MD: –2.69 [95% CI, –4.17 to –1.21], $P < 0.001$).

- IND/GLY reduced the time to a moderate to severe exacerbation versus placebo (HR of 0.56 [95% CI, 0.40 to 0.78], *P* < 0.001) in SHINE.
- There was a statistically significant improvement in symptom scores for IND/GLY versus TIO in SPARK (LS MD of –0.44 [95% CI, –0.62 to –0.26], *P* < 0.001) and in SHINE (–0.24 [95% CI, –0.46 to –0.01], *P* = 0.043).

Harms (Safety and Tolerability)

- The proportion of patients who experienced at least one adverse event was:
  - QUANTIFY: IND/GLY (■%) and TIO (■%).
  - SHINE: IND/GLY (55%), IND (61%), GLY (61%), TIO (57%), and placebo (58%).
  - SPARK: IND/GLY (93%), GLY (94%), and TIO (93%).
  - ILLUMINATE: IND/GLY (55%) and FP/SAL (60%).
  - ENLIGHTEN: IND/GLY (58%) and placebo (57%).
  - BEACON: IND/GLY (26%) and IND + GLY (25%).
- The proportion of patients who experienced at least one serious adverse event was:
  - QUANTIFY: IND/GLY (■%) and TIO (■%).
  - SHINE: IND/GLY (5%), IND (6%), GLY (6%), TIO (4%), and placebo (6%).
  - SPARK: IND/GLY (23%), GLY (24%), and TIO (22%).
  - ILLUMINATE: IND/GLY (5%) and FP/SAL (5%).
  - ENLIGHTEN: IND/GLY (16%) and placebo (11%).
  - BEACON: IND/GLY (4%) and IND + GLY (6%).
- The proportion of patients who withdrew due to adverse events was:
  - QUANTIFY: IND/GLY (■%) and TIO (■%).
  - SHINE: IND/GLY (1%), IND (5%), GLY (3%), TIO (2%), and placebo (4%).
  - SPARK: IND/GLY (11%), GLY (12%), and TIO (9%).
  - ILLUMINATE: IND/GLY (9%) and FP/SAL (10%).
  - ENLIGHTEN: IND/GLY (6%) and placebo (6%).
  - BEACON: IND/GLY (1%) and IND + GLY (1%).

Cost and Cost-Effectiveness

The manufacturer submitted a cost minimization analysis comparing IND/GLY with individually dosed FOR + TIO, IND + GLY, and an FP/SAL combination product in adult patients with COPD who remain symptomatic despite monotherapy with a LABA or LAAC. Comparable efficacy and safety was assumed among treatments based on head-to-head clinical trials.

At the submitted price of $2.68 per 110/50 mcg capsule for inhalation ($1,113 per patient per year, including markup and fees), IND/GLY is less costly than all available combinations of individual LABA and LAAC inhalers ($1,392 to $1,701 per patient per year). If listed, and assuming equivalent efficacy and safety assumptions are valid, IND/GLY would result in annual savings of $280 to $588 per patient when compared with currently available LABA + LAAC combinations. IND/GLY is also less costly ($33 to $766 savings per patient per year) than the currently available ICS/LABA combination products. IND/GLY is more costly than monotherapy LABA or LAAC ($203 to $472 more per patient per year); the manufacturer did not assess the cost-effectiveness of IND/GLY versus monotherapy.

Other Discussion Points:

- QUANTIFY was the only study to compare IND/GLY with another LABA/LAMA (TIO/FOR).
- Formoterol requires twice-daily dosing; therefore, the once-daily dosage regimen of IND/GLY is a potential advantage of this product.

Research Gaps:
- The included studies were not designed or powered to assess treatment differences in mortality and morbidity.
- COPD is a chronic condition and all of the included RCTs were short-term studies.
- Included studies did not address the potential use of IND/GLY as part of a triple therapy regimen in combination with an ICS.

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, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

November 19, 2014 Meeting

Regrets:
None

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

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