CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

INDACATEROL/GLYCOPYRRONIUM/MOMETASONE FUROATE (ENERZAIR BREEZHALER — NOVARTIS PHARMACEUTICALS CANADA INC.)
Indication: Asthma maintenance, adults

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that indacaterol/glycopyrronium/mometasone furoate should be reimbursed for the treatment of asthma in adult patients inadequately controlled with a maintenance combination of a long-acting beta-2 agonist and a medium or high dose of an inhaled corticosteroid, who experienced one or more asthma exacerbations in the previous 12 months, only if the following conditions are met.

Conditions for Reimbursement
The drug plan cost of treatment with indacaterol/glycopyrronium/mometasone furoate should not exceed the drug plan cost of the least costly currently reimbursed medium- or high-dose inhaled corticosteroid and a long-acting beta-2 agonist and a long-acting muscarinic antagonist used singly or in combination.

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Indication: Asthma maintenance, adults

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that indacaterol/glycopyrronium/mometasone furoate should be reimbursed for the treatment of asthma in adult patients inadequately controlled with a maintenance combination of a long-acting beta-2 agonist (LABA) and a medium or high dose of an inhaled corticosteroid (ICS), who experienced one or more asthma exacerbations in the previous 12 months, only if the following conditions are met.

Conditions for Reimbursement

The drug plan cost of treatment with indacaterol/glycopyrronium/mometasone furoate should not exceed the drug plan cost of the least costly currently reimbursed medium- or high-dose ICS and a LABA and a long-acting muscarinic antagonist (LAMA) used singly or in combination.

Reasons for the Recommendation

1. One double-blind, randomized controlled trial (RCT) (IRIDIUM [N = 3,092]) demonstrated that indacaterol/glycopyrronium/mometasone furoate 150 mcg/50 mcg/160 mcg was associated with improved pulmonary function (as measured using trough forced expiratory volume in one second [FEV_1]) as compared with indacaterol/mometasone furoate 150 mcg/320 mcg at 26 weeks.
2. One double-blind, open-label, non-inferiority RCT (ARGON [N = 1,425]) demonstrated that indacaterol/glycopyrronium/mometasone furoate 150 mcg/50 mcg/160 mcg was noninferior to salmeterol/fluticasone propionate 50/500 mcg plus tiotropium 50 mcg for improving health-related quality of life (as measured by the asthma quality of life questionnaire [AQLQ]) at 24 weeks.
3. At the sponsor-submitted price, indacaterol/glycopyrronium/mometasone furoate was less costly and about as effective as salmeterol/fluticasone propionate plus tiotropium. However, there is uncertainty around the cost-effectiveness of indacaterol/glycopyrronium/mometasone furoate relative to other ICS/LABA/LAMA treatments due to the lack of comparative efficacy evidence. Therefore, to be cost-effective, indacaterol/glycopyrronium/mometasone furoate would need to be priced at or below the lowest cost ICS plus LABA plus LAMA alternative.

Implementation Considerations

- Patients should receive training and education in the use of the inhaler device (Breezhaler) to maximize the potential benefits of indacaterol/glycopyrronium/mometasone furoate.
- Asthma exacerbation is defined as: worsening signs or symptoms of asthma (shortness of breath, cough, wheezing or chest tightness and progressive decrease in lung function) requiring administration of systemic corticosteroids for at least three days, or asthma-related hospitalization.

Discussion Points

- Step-down from triple therapy with indacaterol/glycopyrronium/mometasone furoate to ICS/LABA dual therapy may be considered in patients who are not experiencing exacerbations or who are having infrequent and only mild exacerbations; or in patients who are experiencing adverse effects that negate any benefits from triple therapy. There is uncertainty as to the optimal timing to assess treatment step-down; however, clinician expert input suggested step-down could be considered between one and two years of treatment with indacaterol/glycopyrronium/mometasone furoate.

- CDEC discussed the importance of appropriate inhaler use to achieve optimal asthma control and to reduce the occurrence of asthma exacerbations. There is limited comparative evidence between the indacaterol/glycopyrronium/mometasone furoate Breezhaler device and the other available asthma inhaler devices. CDEC noted that existing data are inconclusive in demonstrating a clear advantage on patient preferences, adherence, and correct use with Breezhaler relative to other inhaler devices. Although ARGON compared indacaterol/glycopyrronium/mometasone furoate delivered via the Breezhaler device with salmeterol/fluticasone propionate and tiotropium administered separately via the Diskus and Respimat devices, respectively, the only conclusion that could be drawn was non-inferiority between treatment groups for the change in AQLQ.

Background

Indacaterol/glycopyrronium/mometasone furoate has a Health Canada indication for the maintenance treatment of asthma in adult patients not adequately controlled with a maintenance combination of a LABA and a medium or high dose of ICS who experienced one or more asthma exacerbations in the previous 12 months. Indacaterol/glycopyrronium/mometasone furoate is a LABA, LAMA, and ICS fixed-dose combination. It is available as dry powder (in hard capsules) for oral inhalation and the Health Canada–approved dose is 150 mcg/50 mcg/160 mcg once daily.

Submission History

This is the first indication for which indacaterol/glycopyrronium/mometasone furoate has been reviewed by CADTH and CDEC.

Summary of Evidence Considered by CDEC

CDEC considered the following information prepared by CADTH: a systematic review of RCTs and supportive studies of indacaterol/glycopyrronium/mometasone furoate (150 mcg/50 mcg/160 mcg) and a critique of the sponsor's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience in treating patients with asthma, and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

Two patient groups, the Lung Health Foundation (formerly called the Ontario Lung Association) and Asthma Canada provided input for indacaterol/mometasone furoate. Patient perspectives were obtained by the Lung Health Foundation by telephone interviews with three patients living with asthma (completed in May 2020). Asthma Canada previously conducted in-person interviews (N = 24) and an online survey (N = 200) with adults who have severe asthma (completed in 2014 for the report entitled *Severe Asthma: The Canadian Patient Journey*). Asthma Canada also conducted an online survey with 192 respondents (171 patients with asthma, 21 caregivers, completed May 2020) to gather perspectives about the potential impact of indacaterol acetate/glycopyrronium bromide/mometasone furoate on them. The following is a summary of key input from the perspective of the patient groups:

- Most respondents reported that asthma limited their daily activities and ability to be physically active. Respondents indicated that asthma affected their social activities and interactions with others. Two-thirds of respondents to Asthma Canada's surveys indicated that they felt stigmatized due to their asthma at one point in time. Greater than half of respondents to the Asthma Canada surveys stated that asthma also impacted their attendance and performance at work and school.
- Respondents expressed difficulty achieving control of their asthma and concern about exacerbations leading to emergency room visits and hospitalizations.
- Patients recognize the integral role of the delivery device in achieving optimum benefit from therapy. Difficulty using a device is one of several possible causes of nonadherence to proper administration that may contribute to poor control of their disease.
- Key outcomes identified as important to patients included improved lung function, reduced exacerbations, and a reduction of symptoms such as shortness of breath, coughing, and fatigue. Additionally, patients expressed a desire for higher energy levels and improved ability to exercise, and an increased ability to fight colds and other infections.
- Asthma Canada's survey reported that 45% of respondents wanted easier management of severe asthma through novel medications. The survey also reported that 29% of patients wanted less fear and anxiety in managing their asthma. The Lung Health Foundation interviews identified that patients most often consider administration of medication, side-effects, and financial burden when deciding to try a new medication.

Clinical Trials

The CADTH systematic review section of the CADTH clinical report included two RCTs: IRIDIUM (N = 3,092) and ARGON (N = 1,425). The IRIDIUM study was a phase III multicenter, randomized, double-blind, double-dummy, parallel-group study with a total 52-week treatment period. The ARGON study was a phase IIIb multicenter, randomized, partially-blinded, parallel-group, non-inferiority, open-label active-controlled study with a 24-week treatment period. Both trials included patients that were adults (≥ 18 years old) who had a diagnosis of asthma for at least one year (IRIDIUM) or six months (ARGON) prior to screening. Patients in both studies had to have prior use of a medium- or high-dose LABA/ICS for at least three months and stable doses for at least one month prior to screening, be symptomatic at screening despite treatment (patients with ACQ-7 greater than or equal to 1.5 at the start of the run-in period and at randomization), and have a documented history of one or more asthma exacerbations requiring care from a physician, emergency room visit, or hospitalization in last 12 months prior to screening, and required oral corticosteroids. Lastly, patients needed to have a pre-bronchodilator FEV1 of less than 80% (IRIDIUM) or less than 85% (ARGON) of predicted normal value, and an increase in FEV1 of greater than or equal to 12% and 200 mL within 15 to 30 minutes after administration of salbutamol 400 mcg (or albuterol 360 mcg) at the start of the run-in period.

In IRIDIUM, patients were randomized to one of five treatment groups at a ratio of 1:1:1:1:1, to indacaterol/glycopyrronium/mometasone furoate 150 mcg/50 mcg/160 mcg once daily, indacaterol/glycopyrronium/mometasone furoate 150/50/80 mcg once daily, indacaterol/mometasone furoate 150 mcg/320 mcg once daily, indacaterol/mometasone furoate 150/160 mcg once daily, or salmeterol/fluticasone propionate 50 mcg/500 mcg twice daily.

In ARGON, patients were randomized at a 1:1:1 ratio to one of the three treatment arms: indacaterol/glycopyrronium/mometasone furoate 150 mcg/50 mcg/160 mcg once daily, indacaterol/glycopyrronium/mometasone furoate 150/50/80 mcg once daily, and salmeterol/fluticasone propionate 50 mcg/500 mcg twice daily plus tiotropium 5 mcg once daily (salmeterol/fluticasone propionate plus tiotropium).

The groups randomized to indacaterol/mometasone furoate or indacaterol/glycopyrronium/mometasone furoate containing products were administered treatment via the Breezhaler inhaler device, while salmeterol/fluticasone propionate was administered using the Diskus (or Accuhaler) inhaler device, and tiotropium with the Respimat inhaler device.

Study discontinuation was similar across treatment groups in IRIDIUM, ranging from 5.8% to 6.6%. The most common reason for study discontinuation was patient decision (4.2% to 5.5%). Study discontinuation was not reported for ARGON. Most patients in both studies completed treatment (≥ 89% in all treatment groups).

Several of the outcomes identified in the CADTH systematic review protocol, including outcomes related to asthma exacerbations and health-related quality of life (HRQoL), were reported in the studies. However, only analyses of the primary outcome in both studies and of the key secondary outcome (change in asthma control measured by the ACQ-7) in IRIDIUM were adjusted for multiplicity; all other analyses in both studies may be subject to inflated type I error. The two trials were limited in their generalizability to clinical practice in Canada. Only the IRIDIUM trial included study sites in Canada. Although the inclusion and exclusion criteria of the trials was generally consistent with other asthma clinical trials, patients enrolled in IRIDIUM and ARGON may not representative of patients in Canadian clinical practice, according to the clinical expert consulted by CADTH. The requirement of having to demonstrate bronchodilator reversibility for inclusion in both trials would, in the opinion of the clinical expert, also exclude a proportion of patients who would be considered for treatment with an ICS/LABA/LAMA combination product in practice settings. Lastly, the clinical expert consulted by CADTH noted that FEV1, in isolation, is generally not useful for making decisions regarding the selection of treatments for asthma, and the ACQ-7 is generally not used in clinical practice, particularly by family physicians, who would be expected to be prescribing indacaterol/glycopyrronium/mometasone furoate in clinical practice.

Outcomes

Outcomes were defined a priori in the systematic review protocol of the CADTH clinical report. Of these, CDEC discussed the following: acute asthma exacerbations, change in pulmonary function, HRQoL, asthma control, asthma symptoms, days of missed work or school, health care resource utilization, and harms outcomes. Outcomes related to dyspnea (shortness of breath), patient adherence to treatment, ease of use of treatment and device, and exercise tolerance were not available from the RCTs.

The primary outcome for IRIDIUM was the change from baseline in trough FEV_1 after 26 weeks, which was defined as the average of the two FEV_1 measurements taken 23 hours 15 minutes and 23 hours 45 minutes after the evening dose of treatment. The primary outcome in ARGON was the change from baseline in the AQLQ total score at Week 24.

Efficacy

In IRIDIUM, a numerically greater proportion of patients in the salmeterol/fluticasone propionate treatment group experienced exacerbations (all severities, 50.5%) and severe exacerbations (29.7%) than patients in the indacaterol/glycopyrronium/mometasone furoate (40.2% overall, 21.8% severe) at week 52. In ARGON, a similar percentage of patients in the indacaterol/glycopyrronium/mometasone and salmeterol/fluticasone propionate plus tiotropium groups experienced an exacerbation at 24 weeks (24.2% to 26.5% all severities; [redacted] were severe). Less than [redacted] of patients in any treatment group required hospitalization for an exacerbation in the two studies.

The primary outcome in IRIDIUM, change from baseline in trough FEV_1 at Week 26, demonstrated an improvement with indacaterol/glycopyrronium/mometasone furoate versus indacaterol/mometasone furoate (between group difference of 0.07 L, 95% confidence interval [CI], 0.03 to 0.10; $P < 0.001$) and salmeterol/fluticasone propionate (between group difference of 0.12 L, 95% CI, 0.09 to 0.15; $P < 0.001$). The treatment effect was maintained at Week 52. In ARGON, indacaterol/glycopyrronium/mometasone furoate increased trough FEV_1 relative to salmeterol/fluticasone propionate plus tiotropium with a treatment difference of 0.10 L (95% CI, 0.05 to 0.15) at Week 24.

The primary outcome in ARGON, change from baseline on the AQLQ total score at Week 24, demonstrated non-inferiority of indacaterol/glycopyrronium/mometasone furoate to salmeterol/fluticasone propionate plus tiotropium based on the pre-specified non-inferiority margin of 0.25 points and a treatment group difference in least squares mean of 0.07 points (95% CI, – 0.03 to infinity; $P < 0.001$). In IRIDIUM, the between-group differences in least squares means for change from baseline in AQLQ total score at end of treatment (Week 52) were 0.02 points 95% CI, 0.08 to 0.12) and 0.06 points (95% CI, – 0.04 to 0.16) for the comparisons of indacaterol/glycopyrronium/mometasone furoate versus indacaterol/mometasone furoate and versus salmeterol/fluticasone propionate, respectively.

The treatment difference between indacaterol/glycopyrronium/mometasone furoate and indacaterol/mometasone furoate for the key secondary outcome in IRIDIUM, change from baseline in the ACQ-7 at Week 26, was 0.01 points (95% CI, – 0.07 to 0.09) and between indacaterol/glycopyrronium/mometasone furoate and salmeterol/fluticasone propionate it was – 0.09 points (95% CI, – 0.17 to – 0.01). In ARGON, the between group difference in least squares mean on the ACQ-7 at Week 24 was – 0.12 points (95% CI, – 0.22 to – 0.03) between indacaterol/glycopyrronium/mometasone furoate and salmeterol/fluticasone propionate plus tiotropium.

Harms (Safety)

Adverse events were reported by 74.1% to 78.8% of patients during the 52-week IRIDIUM study and 51.6% to 52.3% of patients during the 24-week ARGON study. Between 3.8% and 9.3% of patients in treatment groups from both studies reported at least one serious adverse event. In IRIDIUM, 2.1% to 3.4% of patients withdrew from treatment due to an adverse event, whereas less than 1% of patients in treatment groups in ARGON. Overall, the frequency of adverse events, serious adverse events, and withdrawals from treatment due to advents did not suggest any imbalances between treatment groups in IRIDIUM and in ARGON.

Seven deaths were reported between the two trials, which were numerically higher in the indacaterol/mometasone furoate treatment group in IRIDIUM (n = 4). Two deaths were reported in the indacaterol/glycopyrronium/mometasone furoate treatment group in IRIDIUM, and one was reported in the salmeterol/fluticasone propionate plus tiotropium treatment group in ARGON. None of the deaths were caused by asthma-related events or considered by the investigators to be related to study drug.

Infections (systemic and local) were the most frequently reported notable harm (45.0% to 53.7% of patients in IRIDIUM and 29.9% to 30.7% of patients in ARGON), followed by local systemic effects (ranged from 5.0% to 11.0% across studies) and cardiovascular disorders (ranged from 2.1% to 9.8% across studies). The frequency of specific adverse events was infrequent and did not suggest any imbalances between treatment groups.

Indirect Treatment Comparisons

The sponsor provided a feasibility report for the purposes of assessing the viability of conducting a network meta-analysis (NMA) between indacaterol/glycopyrronium/mometasone furoate, indacaterol/mometasone furoate, and other dual and triple asthma therapies for the treatment of patient with uncontrolled asthma. The sponsor concluded that conducting an NMA was not feasible due to extensive heterogeneity in the literature, specifically study populations, study duration, and varying definitions of exacerbation. The CADTH assessment of the feasibility report likewise noted the degree of clinical, methods, and statistical heterogeneity that would make conducting an NMA challenging.

Cost and Cost-Effectiveness

The annual per patient drug acquisition cost of indacaterol/glycopyrronium/mometasone furoate (including the Breezhaler device) is $1,251 per year based on a unit cost of $3.43 per capsule.

The sponsor submitted a cost-utility analysis comparing indacaterol/glycopyrronium/mometasone furoate to a dual ICS/LABA inhaler (salmeterol/fluticasone propionate) plus a separate LAMA (tiotropium bromide) (ICS/LABA plus LAMA). The sponsor's analysis was conducted from the perspective of a Canadian publicly funded health care payer over a lifetime time horizon. The pharmacoeconomic submission was based on a Markov model comprised of two health states: day-to-day symptoms and death. Patients in the day-to-day symptom state could experience moderate or severe asthma exacerbations. Patients with severe exacerbations received oral corticosteroids, visited an emergency department, or required admission to hospital, each of which was associated with additional costs and reduced HRQoL. The relative treatment effects (i.e., the rate of moderate and severe asthma exacerbations) were derived from the ARGON trial.

CADTH identified the following key limitations with the sponsor's pharmacoeconomic analysis:

- appropriate comparators were omitted from the sponsor's base case economic model, including other ICS/LABA treatment currently reimbursed on public formularies
- the price of salmeterol/fluticasone propionate was based inappropriately on the brand name version, despite the availability of a generic product
- there was uncertainty as to whether there is a utility benefit associated with indacaterol/glycopyrronium/mometasone furoate, whether it is maintained beyond the clinical trial duration, and whether it is applicable to Canadian patients
- there is limited evidence on the duration of the treatment effect beyond the clinical trial duration
- adverse events were not considered in the sponsor's model, which was deemed inappropriate given that adverse events are associated with the long-term use of high-dose ICS.

CADTH undertook re-analyses to address the identified limitations, including correcting the price of salmeterol/fluticasone propionate and assuming health state utility values to be equivalent across treatments. CADTH was unable to assess the cost-effectiveness of indacaterol/glycopyrronium/mometasone furoate relative to other ICS/LABA plus LAMA treatments, the uncertainty associated with the long-term clinical effectiveness of indacaterol/glycopyrronium/mometasone furoate, or the impact of adverse events on the incremental cost-effectiveness ratio. Given that indacaterol/glycopyrronium/mometasone furoate is less costly than all other alternatives, the cost-effectiveness is dependent on indacaterol/glycopyrronium/mometasone furoate having at least equal clinical efficacy compared to other ICS plus LABA plus LAMA alternatives. Based on CADTH re-analyses, indacaterol/glycopyrronium/mometasone furoate remained less costly and about as effective as salmeterol/fluticasone propionate plus tiotropium (cost savings = $6,674, incremental quality-adjusted life-years gained = 0.0085; in probabilistic sensitivity analyses, indacaterol/glycopyrronium/mometasone furoate was associated with lower health outcomes than salmeterol/fluticasone in 50% of simulations).

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

October 21, 2020 Meeting

Regrets

Three CDEC members did not attend.

Conflicts of Interest

None