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CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

INDACATEROL/MOMETASONE FUROATE (ATECTURA BREEZHALER — NOVARTIS PHARMACEUTICALS CANADA INC.)
Indication: Asthma maintenance (adults, children aged 12 or older)

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that indacaterol/mometasone furoate should be reimbursed for once-daily maintenance treatment of asthma in patients aged 12 years and older with asthma with reversible obstructive airways disease, only if the following conditions are met.

Conditions for Reimbursement
1. It is reimbursed in a manner similar to other fixed-dose combination inhaled corticosteroid/long-acting beta-agonist inhalers indicated for the treatment of asthma.
2. The drug plan cost of treatment with indacaterol/mometasone furoate should not exceed the drug plan cost of the equivalent dose of the least costly inhaled corticosteroid/long-acting beta-agonist inhaler currently reimbursed.

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Indication: Asthma maintenance (adults, children aged 12 or older)

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that indacaterol/mometasone furoate should be reimbursed for once-daily maintenance treatment of asthma in patients aged 12 years and older with asthma with reversible obstructive airways disease, only if the following conditions are met.

Conditions for Reimbursement

1. It is reimbursed in a manner similar to other fixed-dose combination inhaled corticosteroid (ICS)/long-acting beta-agonist (LABA) inhalers indicated for the treatment of asthma.
2. The drug plan cost of treatment with indacaterol/mometasone furoate should not exceed the drug plan cost of the equivalent dose of the least costly ICS/LABA inhaler currently reimbursed.

Reasons for the Recommendation

1. Indacaterol/mometasone furoate, as compared with mometasone furoate alone, demonstrated improvement in asthma control (measured by the change in Asthma Control Questionnaire [ACQ-7] score) and lung function (measured by the change in trough forced expiratory volume in one second [FEV_1]) at week 26 in the PALLADIUM (N = 2,216) double-blind, randomized controlled trial (RCT) and at week 12 in the QUARTZ (N = 802) double-blind RCT.
2. There is no evidence that the combination of indacaterol/mometasone furoate is clinically superior to other combinations of ICS/LABA. Therefore, each low-, moderate-, and high-dose form of indacaterol/mometasone furoate should be priced no more than the least expensive low-, moderate-, and high-dose ICS/LABA fixed-dose alternative for treatment of asthma.

Implementation Considerations

- Patients should receive training and education in the use of the inhaler device (Breezhaler) to maximize the potential benefits of indacaterol/mometasone furoate.

Discussion Points

- The comparative evidence between indacaterol/mometasone furoate and other available ICS/LABA fixed-dose treatments comes from a secondary comparison (without multiplicity adjustment) in the PALLADIUM trial, which indicated that indacaterol/mometasone furoate 150 mcg / 320 mcg daily was noninferior to salmeterol/fluticasone propionate 50 mcg / 500 mcg twice daily for improving pulmonary function (as measured by FEV_1) at week 26.
- Step-down from dual therapy with indacaterol/mometasone furoate to ICS monotherapy should 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 dual therapy. There is uncertainty regarding 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/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/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 the PALLADIUM trial included a secondary comparison between indacaterol/mometasone furoate delivered via the Breezhaler device and salmeterol/fluticasone propionate delivered via the Diskus device, the study did not demonstrate superiority on any of the measured clinical outcomes with indacaterol/mometasone furoate.

- Mometasone furoate is not currently available in the Breezhaler device; it is marketed under the brand name Asmanex in the Twisthaler device. Therefore, patients stepping up from ICS monotherapy with mometasone furoate to ICS/LABA dual therapy with indacaterol/mometasone furoate delivered by the Breezhaler device would need training and education in the use of a different inhaler device.

Background

Indacaterol/mometasone furoate has a Health Canada indication for once-daily maintenance treatment of asthma in adults and adolescents 12 years of age and older with reversible obstructive airways disease. The product monograph notes the following regarding indacaterol/mometasone furoate:

- it should be prescribed for patients not adequately controlled on a long-term asthma medication, such as an ICS, or whose disease severity requires treatment with ICS/LABA
- is not indicated for patients whose asthma can be managed by occasional use of a rapid-onset, short-duration, inhaled beta2-agonist or for patients whose asthma can be successfully managed by ICS along with occasional use of a rapid-onset, short-duration inhaled beta2-agonist
- is not for the relief of acute bronchospasm.

Indacaterol/mometasone furoate is a fixed-dose combination of a LABA and a medium or high dose of ICS, delivered via the Breezhaler inhaler device. It is available as dry powder (in hard capsules) for oral inhalation; the Health Canada–approved doses are 150 mcg / 80 mcg, 150 mcg / 160 mcg, and 150 mcg / 320 mcg.

Submission History

This is the first indication for which indacaterol/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/mometasone furoate (150 mcg / 80 mcg, 150 mcg / 160 mcg, and 150 mcg / 320 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 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*). 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 visits to the emergency room and hospitalizations.
- Patients recognized 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, which 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, improved ability to exercise, and 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 systematic review section of the CADTH clinical report included two double-blind, parallel-group, double- or triple-dummy RCTs of patients with asthma: the QUARTZ (N = 802) and PALLADIUM (N = 2,216) trials. The total duration of the treatment period was 12 weeks in the QUARTZ trial and 52 weeks in the PALLADIUM trial. The two trials enrolled patients who were 12 years of age or older with a diagnosis of asthma that was inadequately controlled (ACQ-7 score of 1.5 or greater at baseline), a pre-bronchodilator FEV_1 greater than 60% and less than 90% (QUARTZ) or greater than 50% and less than 85% (PALLADIUM) of the predicted normal, and who demonstrated bronchodilator reversibility. Patients also had at least one month use of low-dose ICS prior to screening in the QUARTZ trial and at least three months' use of medium- or high-dose ICS or low-dose combination LABA/ICS in the PALLADIUM trial.

In the QUARTZ trial, patients were randomized at a 1:1 ratio to indacaterol/mometasone furoate 150 mcg / 80 mcg once daily or mometasone furoate 200 mcg once daily. In the PALLADIUM trial, patients were randomized at a ratio of 1:1:1:1:1 to one of five treatment groups: indacaterol/mometasone furoate 150 mcg / 160 mcg once daily, indacaterol/mometasone furoate 150 mcg / 320 mcg once daily, mometasone furoate 400 mcg once daily, mometasone furoate 800 mcg once daily, or salmeterol xinafoate/fluticasone propionate (salmeterol/fluticasone propionate) 50 mcg / 500 mcg twice daily. Discontinuation from the double-blind treatment phase was infrequent (9.2% or less) in both of the studies. The most common reason for discontinuation was patient or guardian decision in both the QUARTZ (1.0% to 1.2%) and PALLADIUM (3.9% to 6.8%) trials.

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 but were analyzed outside of the pre-specified statistical testing procedure employed to reduce type I error. The primary outcomes were assessed at 12 weeks in the QUARTZ trial and at 26 weeks in the PALADIUM trial. The duration of the QUARTZ trial may be too short to comprehensively assess asthma control and asthma exacerbations; 52 weeks of treatment and observation is preferred given the seasonal variation in asthma. The PALLADIUM trial was the only study that included a fixed-dose combination ICS/LABA as an active comparator; however, the focus of this comparison was as a secondary non-inferiority analysis comparing the relative effects of each inhaler on trough FEV_1. The two trials were also limited in their generalizability to clinical practice in Canada because the included patient population was not considered representative of patients in Canadian clinical practice. The inclusion criteria regarding bronchodilator reversibility and asthma control (baseline ACQ-7 score of 1.5 or lower) would, in the opinion of the clinical expert consulted by CADTH, exclude a proportion of patients who would be considered for treatment with an ICS/LABA combination product in practice settings. Approximately 8% of patients enrolled in the QUARTZ trial were age 12 to 17 years; therefore, there is limited data on the benefits of indacaterol/mometasone furoate in adolescent patients with asthma. Lastly, the clinical expert consulted by CADTH noted that FEV_1, in isolation, is generally not useful for making decisions regarding the selection of treatments for asthma and that the ACQ-7 is generally not used in clinical practice, particularly by family physicians, who would be expected to be prescribing indacaterol/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 in both trials was the change from baseline in trough FEV_1 (at week 12 in the QUARTZ trial and week 26 in the PALLADIUM trial) for indacaterol/mometasone furoate versus mometasone furoate.

Efficacy

In the QUARTZ trial, 5.1% and 15.0% of patients experienced an asthma exacerbation and [redacted] and [redacted] experienced a severe asthma exacerbation in the indacaterol/mometasone furoate 150 mcg / 80 mcg and mometasone furoate 200 mcg treatment groups, respectively. In the PALLADIUM trial, between [redacted] and [redacted] of patients experienced an asthma exacerbation, and [redacted] to [redacted] experienced a severe exacerbation. [redacted] in the mometasone furoate treatment groups experienced exacerbations (all severities, [redacted] for mometasone furoate 400 mcg and [redacted] for mometasone furoate 800 mcg) and severe exacerbations ([redacted] for mometasone furoate 400 mcg and [redacted] for mometasone furoate 800 mcg) than patients in the indacaterol/mometasone furoate treatment groups (all severities, [redacted] for indacaterol/mometasone furoate 150 mcg / 160 mcg and [redacted] for indacaterol/mometasone furoate 150 mcg / 320 mcg; severe less than [redacted] in both groups). Less than [redacted] of patients in any treatment group experienced an exacerbation requiring hospitalization or permanent discontinuation of the study drug.

Both the QUARTZ and PALLADIUM trials demonstrated an improvement in the change from baseline in trough FEV_1 with indacaterol/mometasone furoate that was statistically significant, with treatment group differences corresponding to low-, medium-, and high-dose indacaterol/mometasone furoate versus mometasone furoate comparisons of 0.18 L (95% CI, 0.15 to 0.22; P < 0.001), 0.21 L (95% CI, 0.17 to 0.26; P < 0.001), and 0.13 L (95% CI, 0.09 to 0.18; P < 0.001), respectively, compared with mometasone furoate. The treatment group difference was maintained at week 52 for the medium and high dose strengths in the PALLADIUM trial.

The comparison of indacaterol/mometasone furoate 150 mcg / 320 mcg to salmeterol/fluticasone propionate 50 mcg / 500 mcg was analyzed for non-inferiority in terms of the primary outcome using a non-inferiority margin of 0.090 L to determine the difference based on the 95% CI. The between-group difference in least squares mean change from baseline for trough FEV_1 was 0.04 L (95% CI, –0.01 to 0.08; P = 0.101), which met the pre-specified non-inferiority threshold.

The treatment group difference on the Asthma Quality of Life Questionnaire (AQLQ) in the QUARTZ trial favoured indacaterol/mometasone furoate by 0.15 points (95% CI, 0.06 to 0.23). In the PALLADIUM trial, the difference between indacaterol/mometasone furoate 150 mcg / 160 mcg and mometasone furoate 400 mcg was 0.19 points (95% CI, 0.08 to 0.30), and 0.08 points (95% CI, –0.03 to 0.19) between indacaterol/mometasone furoate 150 mcg / 320 mcg and mometasone furoate 800 mcg. The difference between the indacaterol/mometasone furoate 150 mcg / 320 mcg and salmeterol/fluticasone propionate 50 mcg / 500 mcg groups on the AQLQ was 0.04 points (95% CI, –0.07 to 0.15).

The key secondary outcome in the QUARTZ and PALLADIUM trials was the change in baseline asthma control as measured by the ACQ-7 score. The treatment group differences corresponding to the low-, medium-, and high-dose indacaterol/mometasone furoate versus mometasone furoate comparisons were –0.22 points (95% CI, –0.29 to –0.14; P < 0.001), –0.25 points (95% CI, –0.33 to –0.16; P < 0.001), and –0.17 points (95% CI, –0.26 to –0.09; P < 0.001), respectively. The PALLADIUM trial was powered to detect a difference in ACQ-7 based on a pooled analysis of indacaterol/mometasone furoate treatment groups (150 mcg / 160 mcg and 150 mcg / 320 mcg) versus mometasone furoate treatment groups (mometasone furoate 400 mcg and mometasone furoate 800 mcg), which was aligned with the analyses of the individual treatment groups with a treatment difference for indacaterol/mometasone furoate versus mometasone furoate of –0.21 points (95% CI, –0.27 to –0.15; P < 0.001) in favour of indacaterol/mometasone furoate. The effects on ACQ-7 between indacaterol/mometasone furoate 150 mcg / 320 mcg and salmeterol/fluticasone propionate 50 mcg / 500 mcg were similar (–0.05 points; 95% CI, –0.14 to 0.03).

Harms (Safety)

Adverse events were reported by 32.3% to 38.3% of patients in the QUARTZ trial and 64.6% to 72.2% of patients in the PALLADIUM trial. Reported serious adverse events were infrequent in the QUARTZ trial (1.8% or less in both treatment groups) and ranged from 5.0% to 8.0% among treatment groups in the PALLADIUM trial (approximately 5% in all treatment groups, except for mometasone furoate 400 mcg, which was 8.0%). Few patients stopped treatment due to adverse events in both the QUARTZ ([redacted]) and PALLADIUM ([redacted]) trials. The most common reason for a serious adverse event or withdrawal due to an adverse event in both studies was asthma, which occurred in less than 2% of patients in each treatment group. One death was reported between the two included studies, which occurred in an adolescent patient in the mometasone furoate 400 mcg treatment group of the PALLADIUM trial. The cause of death was determined by an independent adjudication committee to be due to asthma exacerbation.

In general, the occurrence of specific adverse events was infrequent and did not suggest any imbalances between treatment groups. Infections (systemic and local) were [redacted] reported notable harm ([redacted] of patients in the QUARTZ trial and 49.2% to 76.8% of patients in the PALLADIUM trial), followed by local systemic effects (ranged from 5.0% to 11.0% across studies) and cardiovascular disorders, which occurred in less than [redacted] of patients in the QUARTZ trial, but ranged from 4.6% to 8.3% in the PALLADIUM trial. Local steroid effects, which included cough, oral thrush, nosebleeds, oropharyngeal pain and discomfort, dysphonia, and larynx irritation, occurred in 2.6% to 6.0% of patients across treatment groups in both studies. All other notable harms (as specified in the CADTH systematic review protocol) were reported in 1.1% or fewer patients in any treatment group.

Indirect Treatment Comparisons

The sponsor provided a feasibility report for the purposes of assessing the feasibility of conducting a network meta-analysis (NMA) between indacaterol/mometasone furoate and other dual and triple asthma therapies for the treatment of patients 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, methodological, and statistical heterogeneity that would make conducted an NMA challenging.

Cost and Cost-Effectiveness

The annual per patient cost of indacaterol/mometasone furoate is $707 per year based on a unit cost of $1.94 per capsule (all strengths, including the Breezhaler device).

The sponsor submitted a cost-utility analysis comparing indacaterol/mometasone furoate to salmeterol/fluticasone propionate, a dual combination ICS/LABA inhaler. 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 were 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 PALLADIUM trial, which compared indacaterol/mometasone furoate 150 mcg / 320 mcg and indacaterol/mometasone furoate 150 mcg / 160 mcg to salmeterol/fluticasone propionate 500 mcg / 50 mcg and mometasone furoate 400 mcg and 800 mcg, and the QUARTZ trial, which compared indacaterol/mometasone furoate 150 mcg / 80 mcg to mometasone furoate 200 mcg.

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

- Appropriate comparators were omitted from the sponsor's base case economic; these included other currently available ICS/LABA fixed-dose combination treatments that are currently reimbursed on public formularies.
- Indacaterol/mometasone furoate was compared to mometasone furoate monotherapy, which was considered by CADTH to not represent a relevant comparator because indacaterol/mometasone furoate is intended for patients for whom an ICS/LABA combination treatment is appropriate.
- The price of salmeterol/fluticasone propionate was based inappropriately on the brand name version despite the availability of a generic.
- There was uncertainty about whether there is a utility benefit associated with indacaterol/mometasone furoate and if it is maintained beyond the clinical trial duration and 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.
- The cost-effectiveness of indacaterol/mometasone furoate among adolescents is highly uncertain. The sponsor's analyses were based on adult patients, and the clinical trials on which the effectiveness and utility values were based had enrolled predominantly adult patients.

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. Scenario analyses were undertaken to address the cost-effectiveness of indacaterol/mometasone furoate among patients who require low-, medium-, or high-dose ICS/LABA treatment. CADTH was unable to address the cost-effectiveness of indacaterol/mometasone furoate relative to other ICS/LABA treatments, the uncertainty associated with the long-term clinical effectiveness of indacaterol/mometasone furoate, or the impact of adverse events on the incremental cost-effectiveness ratio (ICER). Based on CADTH re-analyses, indacaterol/mometasone furoate 150 mcg / 80 mcg is not cost-effective at a $50,000 willingness-to-pay threshold for individuals requiring low-dose ICS/LABA (ICER of $2,298,606 per quality-adjusted life-year [QALY] gained). Indacaterol/mometasone furoate 150 mcg / 160 mcg is similarly not cost-effective at a $50,000 willingness-to-pay threshold for those who require medium-dose ICS/LABA treatment (ICER of $1,083,197 per QALY). For those who require high-dose ICS/LABA, indacaterol/mometasone furoate 150 mcg / 320 mcg may be cost saving, providing similar health outcomes at a lower cost than high-dose ICS/LABA.

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

None.

Conflicts of Interest

None.