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CADTH Reimbursement Recommendation

Budesonide / Glycopyrronium / Formoterol Fumarate Dihydrate (Breztri Aerosphere)

Indication: The long-term maintenance treatment to reduce exacerbations of chronic obstructive pulmonary disease (COPD) and treat airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta$_2$-adrenergic agonist or a combination of a long-acting muscarinic antagonist and a long-acting beta$_2$-adrenergic agonist

Sponsor: AstraZeneca Canada Inc.

Final recommendation: Reimburse with conditions

CADTH

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Redactions: Confidential information in this document has been redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Breztri Aerosphere?

CADTH recommends that Breztri Aerosphere be reimbursed by public drug plans for the treatment of chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema if certain conditions are met.

Which patients are eligible for coverage?

Breztri Aerosphere should only be covered to treat patients who are not controlled on optimal dual inhaled therapy for COPD.

What are the conditions for reimbursement?

Breztri Aerosphere should be reimbursed similar to Trelegy Ellipta. The price of Breztri Aerosphere should not exceed the drug program cost with the least-costly fixed-dose inhaled corticosteroid/long-acting muscarinic antagonist/long-acting beta2-agonist (ICS/LAMA/LABA) triple therapy combination for the same indication.

Why did CADTH make this recommendation?

Evidence from 2 trials demonstrated that Breztri Aerosphere significantly reduced the rate of moderate-to-severe exacerbations and improved pulmonary function compared with ICS/LABA and LAMA/LABA therapy combinations for COPD.

There is no evidence to suggest that Breztri Aerosphere is more effective than other reimbursed therapies for the indicated population. Therefore, Breztri Aerosphere should cost no more than the lowest-cost, fixed-dose ICS/LAMA/LABA triple therapy combination. Based on public list prices, the 3-year budget savings is $13.2 million.

Additional Information

What is COPD?

COPD is a chronic lung disease associated with inflammation and obstruction of the airways, most commonly caused by smoking. Symptoms include difficulty in breathing, cough, and flare-ups that might require hospitalization. An estimated 2 million Canadians are living with COPD. COPD is the fifth leading cause of death in Canada.

Unmet needs in COPD

The major unmet needs include a therapy that can improve quality of life and lung function while reducing exacerbations. Patients are also interested in inhalation devices that provide round-the-clock bronchodilation and are easier to use.

How much does Breztri Aerosphere cost?

Breztri Aerosphere's expected cost is $1,545 per patient annually.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that budesonide/glycopyrronium/formoterol (BGF) should be reimbursed for the long-term maintenance treatment of chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Two multi-centre, double-blind, randomized controlled trials (RCTs) (ETHOS [N = 8,588; 52 weeks] and KRONOS [N = 1,902; 24 weeks]) demonstrated that BGF was associated with a statistically significant improvement in the rate of moderate-to-severe exacerbations compared with dual therapies with glycopyrronium/formoterol (both RCTs) and budesonide/formoterol (ETHOS only). BGF was also associated with improved pulmonary function (as measured using trough forced expiratory volume in 1 second [FEV_1]) as compared with budesonide/formoterol and glycopyrronium/formoterol (both RCTs). COPD affects almost all aspects of daily living, and patients are looking for management strategies that can improve lung function and quality of life, reduce exacerbations, delay disease progression, and improve survival. CDEC concluded that BGF may meet some of these needs.

A sponsor-provided indirect comparison suggested that BGF was likely similar in efficacy and safety compared with other ICS/LAMA/LABA therapies for the maintenance treatment for COPD.

BGF ($1,545 per patient annually, sponsor submitted price) is less costly compared with fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) ($1,608 per patient annually, publicly listed price). A cost-minimization analysis was submitted based on the assumption of similar effectiveness of the 2 treatments. As such, BGF should be no more costly than FF/UMEC/VI.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation, renewal, discontinuation, and prescribing	
1. In a similar manner to FF/UMEC/VI.	BGF appeared to have similar efficacy and safety as FF/UMEC/VI based on the sponsor-provided indirect comparison.
Pricing	
2. BGF should not exceed the drug program cost of treatment with the least-costly fixed-dose ICS/LAMA/LABA triple therapy combination reimbursed for the long-term maintenance treatment of COPD, including chronic bronchitis and/or emphysema.	Despite limitations, the sponsor-provided indirect comparison did not demonstrate any difference in efficacy or safety between BGF and other ICS/LAMA/LABA triple therapy combinations. There is insufficient evidence to justify a cost premium for BGF over the least expensive fixed triple therapy combination reimbursed for the treatment of COPD.

Discussion Points

- Recommendations from the Canadian Thoracic Society (CTS) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommend inhaled LAMA/LABA dual therapy as the preferred regimen for most patients with stable COPD experiencing exacerbations, persistent or increased symptoms, exercise intolerance, and/or reduced health status despite the use of LAMA or LABA monotherapy. Clinician expert input indicated that step up to triple therapy with ICS/LAMA/LABA is currently considered in patients with recurrent exacerbations and/or symptoms despite dual bronchodilator therapy.
- CDEC discussed, with clinician expert input, the role of pharmacotherapy step down in the management of COPD. CDEC noted that step down allows physicians to review patient stability and to minimize pharmacological treatments, especially given the potential risk of serious adverse events related to treatment (e.g., increased risk of pneumonia with ICS use). Step down from triple therapy to LAMA/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 1 and 2 years of treatment with triple therapy.
- BGF offers an alternative fixed-dose triple therapy and is administered via metered-dose inhaler (MDI), which may meet the needs of patients who prefer this form of inhaler versus other available options, such as dry powder inhalers. However, CDEC noted that no head-to-head evidence was available to determine whether the BGF MDI results in improved administration, adherence, or outcomes compared with other available fixed-dose triple therapy combinations for COPD.

Background

BGF is a fixed-dose, triple combination therapy of an ICS (budesonide 182 mcg), a LAMA (glycopyrronium [as bromide] 8.2 mcg), and a LABA (formoterol fumarate dihydrate 5.8 mcg). It has a Health Canada indication for the long-term maintenance treatment to reduce exacerbations of COPD and treat airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema who are not adequately treated by a combination of an ICS/LABA or a combination of a LAMA/LABA. BGF is not indicated for the treatment of acute episodes of bronchospasm.

The recommended dosage is 2 oral inhalations twice daily using the Aerosphere MDI device.

Summary of Evidence

To make their recommendation, CDEC considered the following information:

- A clinical review of 2 of RCTs in patients with COPD, and indirect comparison of BGF versus other triple therapies, and a 52-week extension study

- Patients perspectives gathered by 3 patient groups, Chronic Obstructive Pulmonary Disease Association (COPD Canada), the Lung Health Foundation (formerly Ontario Lung Association), and the British Columbia (BC) lung groups
- One clinical specialist with expertise diagnosing and treating patients with COPD
- Input from 1 clinician group, including 3 clinicians from the Division of Respirology at Queen's University
- A review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups who responded to CADTH's call for input and from clinical experts consulted by CADTH for the purpose of this review.

Patient Input

Three patient groups, COPD Canada, the Lung Health Foundation and the BC lung groups, provided input to this submission. Patient perspectives were obtained from group sessions, interviews, and surveys. The following is a summary of key input from the perspective of the patient groups.

COPD affects almost all aspects of daily living, such as the ability to breathe, talk, sleep, work and socialize. As the disease progresses and worsens, patients become less physically active and more socially isolated. Caregivers face considerable challenges that commonly include: limited time for managing their own health and well-being; feelings of depression and isolation; anxiety, stress, and fatigue; and increased requirements for social support.

Exacerbations are a concern for patients, as they are associated with both short- and long-term consequences on overall health, such as a decline in lung function, greater anxiety, worsening quality of life, social withdrawal, more exacerbations, and increased risk of hospitalization and mortality.

Current therapies for COPD provide some relief of symptoms, but their effectiveness diminishes over time. A variety of 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. Patients indicated that the diminishing effectiveness with the long-term use of some medications should be addressed, and that therapies that offer a convenient treatment option for COPD patients who require long-term maintenance therapy are desirable. The patient groups noted that BGF would be a welcomed addition to provincial formularies across the country.

Clinician Input

Input from clinical experts consulted by CADTH

The expert noted that a triple therapy combination therapy with an MDI and spacer device would be beneficial to patients, particularly if they are already administering their rescue medications as an MDI and a spacer. The expert pointed out that the pharmacological

components of BGF are familiar to physicians and the place in therapy for triple therapy is established per CTS and GOLD guidelines.

Clinician group input

Three clinicians from the COPD clinic in the Division of Respirology at Queen's University provided input. The group noted that a stepwise adding approach was used in COPD management in clinical settings. They pointed out that COPD patients who experience frequent exacerbations despite being on dual therapies would be the group that may benefit the most from BGF. The clinicians added that fixed-dose triple therapy combinations, such as BGF, would likely improve the deposition of the bronchodilators and ICS in the target location leading to better ventilated alveolar units and better outcomes for the patient.

Drug program input

The drug programs asked about the appropriate comparators for assessing the efficacy of BGF. The clinical expert noted that while dual therapies (i.e., ICS/LAMA or LAMA/LABA) can be used to establish efficacy of BGF, other triple therapy combinations (fixed dose or other) would be the most appropriate comparators.

Clinical Trials

The CADTH systematic review included 2 multisite, double-blind, parallel group, randomized, placebo-controlled trials, ETHOS and KRONOS. ETHOS was a 52-week trial that enrolled patients were COPD (age 40 to 80 years) who were receiving maintenance therapy for at least 6 weeks and had a documented history of at least 1 COPD exacerbation within the previous year. Overall, 8,588 patients were enrolled and randomized to receive BGF MDI 320 mcg/14.4 mcg/9.6 mcg twice daily; BGF MDI 160 mcg/14.4 mcg/9.6 mcg twice daily; BFF MDI 320 mcg/9.6 mcg twice daily; or GFF MDI 14.4 mcg/9.6 mcg twice daily. All treatments were administered with the Aerosphere MDI device. Among them, the treatment of BGF MDI 160 is not aligned with the Health Canada recommended dosage and was not considered for review. Outcomes of the ETHOS trial included the rate of moderate-to-severe COPD exacerbations (primary end point), severe COPD exacerbations, symptoms, health-related quality of life, pulmonary function, use of rescue inhaler medication, all-cause mortality, and safety.

KRONOS was a 24-week trial and eligible patients had COPD (age 40 to 80 years) and who were receiving maintenance therapy for at least 6 weeks before study start. Overall, 1,902 patients were randomized (1,899 treated) to receive BGF MDI 320 mcg/14.4 mcg/9.6 mcg twice daily, GFF MDI 14.4 mcg/9.6 mcg twice daily, BFF MDI 320 mcg/9.6 mcg twice daily, or budesonide/formoterol dry powder inhaler (BUD/FOR DPI) via Symbicort Turbuhaler 400 mcg/12 mcg. The BUD/FOR DPI was administered as open label. The KRONOS study had similar outcomes to the ETHOS trial, including rate of moderate-to-severe COPD exacerbations, symptoms, health-related quality of life, use of rescue inhaler medication, and safety. Change in pulmonary function based on FEV_1 was the primary outcome.

Efficacy

Exacerbations

In ETHOS, the adjusted rates of moderate or severe exacerbations per year were 1.08, 1.42 and 1.24 for BGF MDI 320 mcg, GFF MDI and BFF MDI arm respectively. The rate difference between BGF MDI 320 and GFF MDI was −0.35 (95% CI, −0.46 to −0.23) and between BGF MDI 320 and BFF MDI it was −0.17 (95% CI, −0.27 to −0.06). In KRONOS, the adjusted

annualized rates of moderate or severe exacerbations per year were numerically lower for BGF MDI 320 mcg (0.46) compared to GFF MDI (0.95), BFF MDI (0.56) and BUD/FOR DPI (0.56); however, rate differences were not reported.

BGF MDI 320 mcg was associated with significantly lower rates of moderate or severe COPD exacerbations compared to GFF MDI (rate ratio = 0.76 [95% CI, 0.69 to 0.83] at 52 weeks, ETHOS and 0.48 [95% CI, 0.37 to 0.64] at 24 weeks, KRONOS), and BFF MDI at 52 weeks (rate ratio = 0.87 [95% CI, 0.79 to 0.95], ETHOS) There was no statistically significant difference in the rate of moderate-to-severe exacerbation as found by KRONOS trial between BGF MDI and BUD/FOR DPI (rate ratio = 0.83 [95% CI, 0.59 to 1.18]) as well as BFF MDI (rate ratio = 0.82 [95% CI, 0.58 to 1.17) at 24 weeks.

Lung function

Lung function, measured as FEV_1 $AUC_{0\ to\ 4}$ over 24 weeks, was the primary outcome for the comparisons BGF MDI 320 versus BFF MDI (ETHOS and KRONOS) and BGF MDI 320 versus BUD/FOR DPI (KRONOS). In ETHOS, this outcome was assessed in a pulmonary function test (PFT) substudy population. BGF MDI 320 showed a statistically significant improvement in lung function compared to both BFF MDI (least squares mean [LSM] = 104 mL; 95% CI, 77 to 131) and BUD/FOR DPI (LSM = 91 mL; 95% CI, 64 to 117). Based on a minimal clinical important difference (MCID) of 100 mL to 140 mL, these differences were likely clinically significant. Lung function measured as morning pre-dose trough FEV_1 over 24 weeks was the primary outcome for the comparisons BGF MDI 320 mcg versus GFF MDI (ETHOS and KRONOS). In ETHOS, this outcome was assessed in a PFT substudy population. The change from baseline in morning pre-dose trough FEV_1 at 24 weeks for BGF MDI 320 mcg compared to GFF MDI was not clinically significant (22 mL; 95% CI, 4 to 39).

Use of rescue medication

In both trials, the evaluation of average daily number of puffs of rescue medication over 24 weeks was restricted to the rescue inhaler use population. In ETHOS, BGF MDI 320 was associated with a statistically significant reduction in the use of rescue medication compared to GFF MDI (difference = −0.51 puffs/day; 95% CI, −0.68 to −0.34) and BFF MDI (difference = −0.37 puffs/day; 95% CI, −0.54 to −0.20). No statistically significant differences were found between the groups in KRONOS.

Symptoms

The change from baseline of the Transition Dyspnea Index (TDI) focal score was used by both trials to assess improvement in dyspnea symptoms with treatment. Although both trials found that BGF MDI improved the symptoms compared to GFF MDI, BFF MDI and BUD/FOR DPI, these were not clinically significant improvements. In ETHOS, the difference in LSM of TDI focal score in BGF MDI 320 mcg compared to GFF MDI were 0.40 units (95% CI, 0.24 to 0.55) and compared to BFF MDI were 0.31 units (95% CI, 0.15 to 0.46). In KRONOS, the difference in LSM of TDI focal score in BGF MDI 320 versus GFF MDI was 0.177 units (95% CI, −0.071 to 0.426); BGF MDI 320 versus BFF MDI was 0.237 units (95% CI, −0.068 to 0.542) BGF MDI 320 mcg versus BUD/FOR DPI was 0.461 units (95% CI, 0.156 to 0.766). There were no clinically meaningful improvements in symptoms BGF MDI compared to other groups, as measured using the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) or Evaluating Respiratory Symptoms in COPD (E-RS).

Health-related quality of life (HRQoL)

St. George's Respiratory Questionnaire (SGRQ) was used to measure HRQoL in in both trials. Patients in all treatment groups showed clinically significant improvement in SGRQ total score before and after treatment. However, between groups, these improvements were not clinically significant (MCID = 4 units). In ETHOS, the mean difference in SGRQ total score was −1.62 units (95% CI, −2.27 to −0.97) for BGF MDI versus GFF MDI and −1.38 (95% CI, −2.02 to −0.73) for BGF MDI 320 mcg versus BFF MDI. These differences were statistically significant, but not clinically meaningful. In KRONOS, the mean differences were −1.22 units (95% CI, −2.30 to −0.15) and −0.45 units (95% CI, −1.78 to 0.87) for BGF MDI versus GFF MDI and BGF MDI versus BFF MDI respectively.

Mortality

All-cause mortality was evaluated by ETHOS (as a secondary outcome) but not KRONOS. The risk of death (all cause) was lower during treatment with BGF MDI 320 relative to GFF MDI (hazard ratio = 0.51; 95% CI, 0.330 to 0.80), but not different relative to BFF MDI (HR = 0.72; 95% CI, 0.44 to 1.16) as assessed by the Cox proportional hazards model.

Harms (Safety)

Within each trial, adverse events were similar across treatment arms. Most common treatment-associated adverse events were COPD, (9.5% to 11.3% in ETHOS; 2.5% to 5.1% in KRONOS), nasopharyngitis (9.4% to 11% in ETHOS; 7.7% to 9.4% in KRONOS) and upper respiratory tract infections (4.8% to 5.7% in ETHOS; 5.7% to 10.2% in KRONOS). Around 20% of patients in ETHOS and 9% of those in KRONOS reported 1 or more serious adverse events. Incidence of pneumonia was 1.6% to 2.8% in ETHOS and 0.0% to 1.3% in KRONOS. In ETHOS, there were a total of 111 (1.3%) patients with an adverse event with a fatal outcome; whereas in KRONOS, 12 (0.6%) patients in total died based on the safety population.

Around 6% of patients in ETHOS and 4% of patients in KRONOS withdrew due to adverse events. Notable harms such as cardiovascular events, anticholinergic events and corticosteroid-related events were reported in a small number of patients in each trial. The incidences were relatively similar across treatment arms.

Critical Appraisal

[redacted] The relatively high rates of treatment discontinuation (22% in ETHOS and 14% KRONOS) could have biased the results in favour of BGF. The BUD/FOR DPI arm in KRONOS was open label, which could have introduced a subjective bias in patient-reported outcomes. The chances of inadvertent unblinding due to adverse events were low given the similarities in the events across the treatment groups. The degree and type of training provided for the inhaler device was not described in the trials. However, the treatment adherence was high across the treatment arms in both trials, measured by the ratio of daily puffs taken and the expected number of daily puffs. The choice of comparator (LAMA/LABA or ICS/LABA) could have biased the outcomes to BGF since usual treatment for patients experiencing symptoms and exacerbations is to step up to triple therapy and some patients randomized to dual therapy had been treated with triple therapy before entry to the trials.

There were several limitations related to generalizability compared to Canadian COPD population, such as lower proportion of female participants, lower proportion of patients

with treatment history with LAMA/LABA, and a higher proportion of patients with ICS use at baseline. Some outcomes, which were pointed out as important by the patient groups, were not considered in the trials such as exercise tolerance and patient satisfaction outside items within SGRQ.

Indirect Evidence

One network meta-analysis (NMA), submitted by the sponsor, was identified to provide indirect evidence. The NMA compared BGF MDI 320 mcg with other open and fixed triple therapy combinations of ICS/LAMA/LABA for the treatment of moderate-to-severe COPD. Systematic literature search, study selection, and quality assessments were conducted appropriately. For the NMA analysis, all LAMA/LABA combinations were grouped together as a single node to create networks and an assumption of similar efficacy was made. Analyses were conducted using 3-level hierarchical Bayesian NMA models.

The population, intervention, comparators, and outcomes considered by the NMA were relevant. Fifteen double-blinded RCTs were included in the NMA. The baseline characteristics of the study participants and results of the included studies were not reported, making the interpretation across trials regarding potential effect modifiers and homogeneity challenging. Despite the important limitations, the results of the NMA suggested similar efficacy and safety between BGF MDI 320 mcg, FF/UMEC/VI, and open triple therapy combinations.

Other Relevant Evidence

The KRONOS extension study was a 52-week study that evaluated the safety and effects of BGF on bone mineral density and ocular outcomes in patients with moderate-to-severe COPD. Overall, 456 patients were included in the safety population and were randomized to 1 of the treatment groups: BGF MDI, BFF MDI, or GFF MDI. Changes from baseline in all 3 groups were small and not clinically meaningful, and there no new or unexpected adverse events observed. Given the outcomes chosen, the main limitations for the extension safety study were the study duration and the relatively small sample size.

Cost and Cost-Effectiveness

At the submitted price of $127.00 per 120-dose inhaler, the average annual cost of treatment BGF is $1,545 per patient. Assuming equal efficacy and safety with FF/UME/VI and with available ICS/LABA plus LAMA combinations, the sponsor conducted a cost-minimization analysis over a 1-year time horizon comparing the costs of BGF to FF/UME/VI and a weighted-average cost of available ICS/LABA plus LAMA combinations.

CADTH identified the following limitations with the sponsor's submission:

- the assumption of clinical similarity between comparators is associated with some uncertainty
- the use of a weighted-average class comparator was inappropriate
- LABA/LAMA + ICS combinations are potentially relevant comparators in some jurisdictions.

When considering only drug costs (i.e., excluding dispensing fees and markups), and assuming similar efficacy and safety among included comparators, the annual per patient drug acquisition cost of BGF ($1,545) is $63 less expensive than FF/UME/VI ($1,608) and

$200 less than BUD/FOR plus glycopyrronium ($1,745) – the combination of 2 inhalers with the same component medications as BGF. When considering dispensing fees and markups (based on Ontario estimates), the annual cost of BGF ($1,776 per patient) is $237 more than that of the least expensive ICS/LABA plus LAMA combination (range: $1,580 to $2,888 per patient). The use of a single inhaler for triple therapy is associated with a reduction in dispensing fees compared to combinations of 2 inhalers, potentially saving 12 fees per year when dispensed monthly. Of note, all analyses are based on publicly available list prices and may not represent actual costs paid by plans.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: uncertainty in the relative market shares of comparators, potentially missing comparators of interest, uncertainty in displacement assumptions, and a reliance on publicly listed prices for comparators. CADTH did not conduct base-case reanalyses, instead accepting the sponsor's estimated budgetary savings associated with the reimbursement of BGF of $13.2 million over 3 years when considering only drug costs, or $20.6 million over 3 years when including markups and dispensing fees as the best estimate given the available data. However, the presence of confidential prices paid by the jurisdictions is likely to reduce or eliminate these savings, depending on the discounts in place.

Members of the Canadian Drug Expert Committee

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, Dr. Kerry Mansell, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Meeting date: June 16, 2021

Regrets: Three members did not attend

Conflicts of interest: None