CADTH

CADTH REIMBURSEMENT REVIEW

Clinician Input

BUDESONIDE/GLYCOPYRRONIUM/FORMOTEROL FUMARATE (Breztri Aerosphere)

(AstraZeneca Canada Inc.)

Indication: Chronic obstructive pulmonary disease (COPD)

February 22, 2021

CADTH Drug Reimbursement Review
Clinician Group Input Template

CADTH Project Number	**SR0675-000**
Generic Drug Name (Brand Name)	**budesonide/ glycopyrronium /formoterol fumarate**
Indication	**COPD**
Name of the Clinician Group	**Division of Respirology, Queen's University: COPD outpatients clinic**
Author of the Submission	**J Alberto Neder, MD, PhD, DSc, FRCP(C)**
Contact information	Name: J Alberto Neder Title: Professor, Respiratory Medicine Email: [redacted] Phone [redacted]

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

Research-intensive, university-based academic center. Research, teaching and long-term care (including rehabilitation) of patients with COPD.

https://deptmed.queensu.ca/divisions/respirology

The opinion herein presented represents the view of the participants and does not reflect the views of the whole Division or the Department of Medicine or Queen's University or the Kingston Health Science Center.

2. Information Gathering

Please describe how you gathered the information included in the submission.

Peer-reviewed paper, recent reviews and updates on the topic up to February 9th 2021 .

All members regularly see patients with mild to end-stage COPD, being active researchers with extensive lecturing experience in clinical issues involving patients with COPD.

3. Current treatments

3.1. Describe the current treatment paradigm for the disease

Smoking cessation, anti-influenza/anti-pneumococcal vaccination, regular physical activity (or pulmonary rehabilitation in more dyspneic patients), and short-acting bronchodilators p.r.n. are recommended regardless of the disease severity. Addressing co-morbidities is paramount, including chronic rhinosinusitis, GERD, sleep disorder breathing, and ischemic heart disease, amongst others (*O'Donnell DE, Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease - 2007 update. Can Respir J. 2007 Sep;14 Suppl B(Suppl B):5B-32B*)

A stepwise, adding-up approach to long-acting bronchodilators is applied to more symptomatic patients (at least Grade 1 according to the mMRC scale), usually starting with a long-acting antimuscarinic (LAMA) in isolation followed by a LAMA-long-acting beta-2 adrenoceptor agonist (LABA) combination if monotherapy is deemed insufficient for adequate symptom control (at least Grade 2 according to the mMRC scale).() Low-to-moderate doses of inhaled corticosteroids (ICS) are added to LABA or LAMA-LABA in frequent exacerbators (≥2 "moderate" exacerbations which prompted a prescription of antibiotics and/or oral steroids or at least 1 "severe" exacerbation which required hospitalization or ED visit in the last year) with some physicians relying on eosinophil counts to decide for an ICS (e.g., ≥300 μL). (*Alter et al. Update in Chronic Obstructive Pulmonary Disease 2019/ Am J Respir Crit Care Med . 2020 Aug 1;202(3):348-355.). O*ral theophylline is used in some patients with advanced disease as well as low-dose oral opiates and anxiolytics in selected patients. Macrolide prophylaxis (*Janjua S. Prophylactic antibiotics for adults with chronic obstructive pulmonary disease: a network meta-analysis. Cochrane Database Syst Rev 2021 Jan 15;1:CD013198. doi: 10.1002/14651858.CD013198.pub2*), oral N-acetylcysteine and roflumilast might be used to further decrease the frequency and severity of exacerbations. Action plans, usually containing a respiratory fluoroquinolone and oral steroids, are made available to well-educated patients *(Criner GJ, et al. Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society Guideline. Chest. 2015 Apr;147(4):894-942.)* Long-term oxygen therapy is considered for hypoxemic patients (either rest or exercise) whereas non-invasive positive pressure ventilation might be helpful in hypercapnic patients(*Wilson ME et al. Association of home noninvasive positive pressure ventilation with clinical outcomes in chronic obstructive pulmonary disease: a systematic review and meta-analysis. JAMA. 2020;323:455-65. 32016309*). Bullectomy and lung volume reduction (either surgery or endoscopy-based) are restricted to carefully selected patients. Eligible patients with end-stage disease might be referred for lung transplantation (*2020 (Global Strategy for Prevention, Diagnosis and Management of COPD.* https://goldcopd.org/gold-reports/. Accessed on February 6th 2021).

No treatment modifies the underlying disease mechanism, being fundamentally focused on reducing the burden of moderate-to-severe exacerbations and dyspnea control.

4. Treatment goals

4.1. What are the most important goals that an ideal treatment would address?

Improve dyspnea (particularly activity-related), reduce the burden of moderate to severe acute exacerbations, decrease the rate of lung function decline, and improve health-related quality of

life.(*2020 Global Strategy for Prevention, Diagnosis and Management of COPD.* https://goldcopd.org/gold-reports/. Accessed on February 6th 2021) More recently, improving survival has been considered a potential target.

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Highly-variable response as pertaining to dyspnea control.. Reduced efficacy in controlling exacerbations in those who are more in need of, i.e., the "frequent exacerbators". Important limitations in drug delivery to the smaller airways. Shortcomings in the activation of dry powder inhalers (DPIs) due to insufficient peak inspiratory flows in more hyperinflated patients. Poor "round-the-clock" bronchodilatation in OD medications. Absence, in the Canadian market, of triple therapy BID (more consistent bronchodilatation day and night) delivered by a MDI (better airway deposition). Convenience (e.g., OD versus BID) is not usually an issue in chronically dyspneic patients who do derive sensory benefit from long-acting bronchodilators (*authors' experience*). Apart for smoking cessation and long-term O_2 therapy in hypoxemic patients, no treatments are available to consistently reverse the course of disease.

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

COPD patients (either emphysema or chronic bronchitis) who are frequent exacerbators (as defined in 3.1) despite being on dual therapies (LABA-ICS or LAMA-LABA), particularly (but not only) if reporting at least moderate dyspnea on daily life (mMRC≥2). The drug combination under review does address this important unmet need (*Martinez FJ, et al Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD. N Engl J Med. 2020 Jul 2;383(1):35-48*.). There is also recent evidence that the drug combination under review may also decrease the exacerbation burden even in patients who did not present with a recent (one year before) exacerbation history (*Martinez et al. Budesonide/Glycopyrrolate/Formoterol Fumarate Metered Dose Inhaler Improves Exacerbation Outcomes in Patients with COPD without a Recent Exacerbation History: A Subgroup Analysis of KRONOS. Int J Chron Obstruct Pulmon Dis. 2021 Jan 28;16:179-189. doi: 10.2147/COPD.S286087*). Additional considerations are made relative to the current product in 6.2 as a potential first treatment option.

6. Place in therapy

6.1. How would the drug under review fit into the current treatment paradigm?

As detailed in 3.1, triple therapy in a single inhaler complements the foundations of COPD treatment (smoking cessation, anti-influenza/anti-pneumococcal vaccination, regular physical activity (or pulmonary rehabilitation in more dyspneic patients), and short-acting bronchodilators p.r.n) . There is another triple therapy in the Canadian market (umeclidinium, vilanterol and fluticasone furoate (UVFF). However, this product is administered OD through a DPI. Drug delivery and insufficient bronchodilation over the 24 hours are major concerns. Moreover, fluticasone has been associated with a higher rate of bacterial pneumonia compared to budesonide *(Mattishent K, et al. Meta-review: adverse effects of inhaled corticosteroids relevant to older patients Drugs 2014 Apr;74(5):539-47. doi: 10.1007/s40265-014-0202-z).* Formoterol is a dual short-and long-acting bronchodilator with a faster onset of action compared to vilanterol,

leading to a quicker relief of dyspnea (*Maltais F et al. A Randomized, Double-Blind, Double-Dummy Study of Glycopyrrolate/Formoterol Fumarate Metered Dose Inhaler Relative to Umeclidinium/Vilanterol Dry Powder Inhaler in COPD. Adv Ther 2019 Sep;36(9):2434-2449). T*hus, for more symptomatic patients, UVFF is frequently insufficient for dyspnea control (*authors' experience*).

The drug combination under review can be used either after a trial of LABA-ICS (preferentially) or.LAMA-LABA (*2020 (Global Strategy for Prevention, Diagnosis and Management of COPD.* https://goldcopd.org/gold-reports/. Accessed on February 6th 2021) OR as a first line treatment in patients with a particularly high burden of moderate-to-severe exacerbations as detailed in 6.2 (*authors' perspective*).

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

A standard recommendation on this regard is not appropriated due to the large heterogeneity of the disease. Whereas the use of LABA-ICS (or, less likely, LAMA-LABA) might be defensible in some patients who barely meets the criteria for "frequent exacerbators, the available evidence clearly indicates that triple therapy (LAMA/LABA/ICS) is superior to dual therapies (LAMA/LABA and ICS/LABA) in reducing the burden of moderate to severe exacerbations whilst improving dyspnea to the same extent than LAMA/LABA. (*Martinez FJ, et al Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD. N Engl J Med. 2020 Jul 2;383(1):35-48; Martinez FJ, et al. Reduced All-Cause Mortality in the ETHOS Trial of Budesonide/Glycopyrrolate/Formoterol for COPD: A Randomized, Double-Blind, Multi-Center Parallel-Group Study. Am J Respir Crit Care Med. 2020 Nov 30. doi: 10.1164/rccm.202006-2618OC).* It follows that triple therapy might be the more appropriate first choice for some patients with an unordinary burden of moderate-to-severe exacerbations who are at high risk of a negative outcome if a major exacerbation occurs. The likelihood of a negative, life-threatening outcome is usually decided on a patient-by-patient basis, involving the severity of functional impairment, previous history of life-threatening exacerbations (including ICU admission) and the severity of co-morbidities (particularly cardiovascular disease) (*authors' perspective*).

6.3. How would this drug affect the sequencing of therapies for the target condition?

As mentioned in 6.2, triple therapy might be the more appropriate first choice (compared to LAMA-LABA or LABA-ICS) for some patients with a particularly high burden of moderate-to-severe exacerbations who are at high risk of a negative outcome if a major exacerbation occurs. The likelihood of a negative, life-threatening outcome is usually decided on a patient-by-patient basis, involving the severity of functional impairment, previous history of life-threatening exacerbations (including ICU admission) and the severity of co-morbidities (particularly cardiovascular disease). In this context, the current medication might be considered an option without the need of a previous use of LABA-LAMA or LABA-ICS (*authors' perspective*).

6.4. Which patients would be best suited for treatment with the drug under review?

COPD patients presenting with a high burden of moderate to severe exacerbations ((≥2 "moderate" exacerbations which prompted a prescription of antibiotics and/or oral steroids or at least 1 "severe" exacerbation which required hospitalization or ED visit in the last year). These patients are more in need of an intervention (*Martinez FJ, et al Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD. N Engl J Med. 2020 Jul 2;383(1):35-48; Martinez FJ, et al. Reduced All-Cause Mortality in the ETHOS Trial of Budesonide/Glycopyrrolate/Formoterol for COPD: A Randomized, Double-Blind, Multi-Center Parallel-Group Study. Am J Respir Crit Care Med. 2020 Nov 30. doi: 10.1164/rccm.202006-2618OC*). Interestingly, however, recent data indicated that this drug combination is also effective in delaying moderate-to-severe exacerbations even in those without a recent (last year) exacerbation (*Martinez et al, Budesonide/Glycopyrrolate/Formoterol Fumarate Metered Dose Inhaler Improves Exacerbation Outcomes in Patients with COPD without a Recent Exacerbation History: A Subgroup Analysis of KRONOS. Int J Chron Obstruct Pulmon Dis. 2021 Jan 28;16:179-189.)* The presence of at least moderate dyspnea on daily life (at least Grade 2 according to the mMRC scale) strengthen the indication but it should not be considered *sine qua non*.

6.5. How would patients best suited for treatment with the drug under review be identified?

The diagnosis of chronic, poorly-reversible airflow limitation on spirometry is mandatory. Spirometry alone might underestimate the severity of functional impairment; thus, measurements of lung volumes and lung diffusing capacity might be warranted in patients with out-of-proportion dyspnea (*Neder JA, et al, Lung Function Testing in Chronic Obstructive Pulmonary Disease. Clin Chest Med. 2020 Sep;41(3):347-366.)* Under-diagnosis due to the lack of pulmonary function tests is common but, once available, the diagnosis is usually straightforward in a patient with high pre-test likelihood of disease, i.e., smoker or ex-smoker, aged 40 or older. Clinical history is crucial to identify the frequent exacerbators and patients reporting higher dyspnea burden (*2020 Global Strategy for Prevention, Diagnosis and Management of COPD.* https://goldcopd.org/gold-reports/. Accessed on February 6th 2021). Blood eosinophils might provide auxiliary information. There is not sufficient evidence to indicate that treatment with triple therapy should be considered in pre-symptomatic COPD.

6.6. Which patients would be least suitable for treatment with the drug under review?

Patients with a low burden of exacerbations (≤1 moderate exacerbation without a severe exacerbation in the preceding year) (*Mammen M, et al. Triple Therapy versus Dual or Monotherapy with Long-Acting Bronchodilators for Chronic Obstructive Pulmonary Disease. A Systematic Review and Meta-analysis. 2020 Oct;17(10):1308-1318. doi: 10.1513/AnnalsATS.202001-023OC)* and patients with mild dyspnea (mMRC dyspnea grade ≤1) with LAMA and/or LABA and/or short acting bronchodilators.

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

Clinical history (dyspnea burden and dyspnea on daily life) and, occasionally, circulating eosinophilia. The severity of functional impairment on pulmonary function tests might also influence some treatment choices (see 6.2).

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Frequency and severity of COPD exacerbations and dyspnea on daily life (*2020 Global Strategy for Prevention, Diagnosis and Management of COPD.* https://goldcopd.org/gold-reports/. Accessed on February 6th 2021).
6.9. What would be considered a clinically meaningful response to treatment?
Absence of severe exacerbations and ≤ 1 moderate exacerbation in the year subsequent to treatment initiation. Secondarily, improvement in at least one grade in the mMRC dyspnea score and a lower use of short-acting bronchodilators prn). The magnitude of the treatment effect can be assessed by any physician.
6.10. How often should treatment response be assessed?
1-2 months after treatment initiation to assure compliance and lack of side effects. Thereafter, every 6 months is likely appropriate for most patients (*2020 Global Strategy for Prevention, Diagnosis and Management of COPD.* https://goldcopd.org/gold-reports/. Accessed on February 6th 2021) This might be shortened in the presence of repetitive exacerbations/use of an action plan despite adherence to treatment.
6.11. What factors should be considered when deciding to discontinue treatment?
Once triple therapy is initiated in a patient with clear indication(s) there is conflicting evidence on whether it is safe or not to de-escalate to LABA-LAMA or LABA-ICS after exacerbation control (REFS). This is more likely to be safely accomplished by a specialist (respirologist) on a patient-by-patient basis (*Magnussen H. et al. Withdrawal of inhaled corticosteroids versus continuation of triple therapy in patients with COPD in real life: observational comparative effectiveness study. Respir Res 2021 Jan 21;22(1):25. doi: 10.1186/s12931-021-01615-0*.).
6.12. What settings are appropriate for treatment with the drug under review?
Community setting, outpatient clinic, specialty clinic
6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?
For most patients, this is not necessary (provide the family physician reviews the patient with regularity). However, a respirologist or a COPD NP might better monitor more severe patients with several hospital admissions and frequent ED visits, and those who require multiple interventions such as long-term O_2 therapy, non-invasive ventilation, opiates for dyspnea control, etc. (*2020 Global Strategy for Prevention, Diagnosis and Management of COPD.* https://goldcopd.org/gold-reports/. Accessed on February 6th 2021.)
7. Additional information
7.1. Is there any additional information you feel is pertinent to this review?
The authors call the attention of the reviewing committee for recent data showing a positive effect of LAMA-LABA-ICS on a single device (including the product under review) on all-cause and respiratory mortality in patients with COPD presenting with a history of moderate to severe exacerbations. Of note, this was observed in two large randomized and control trials (*Lipson DA,*

***et al. Reduction in All-Cause Mortality with Fluticasone Furoate/Umeclidinium/Vilanterol in Patients with Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2020 Jun 15;201(12):1508-1516. doi: 10.1164/rccm.201911-2207OC; Martinez FJ, et al. Reduced All-Cause Mortality in the ETHOS Trial of Budesonide/Glycopyrrolate/Formoterol for COPD: A Randomized, Double-Blind, Multi-Center Parallel-Group Study. Am J Respir Crit Care Med. 2020 Nov 30. doi: 10.1164/rccm.202006-2618OC*). The signal (in both studies) was particularly strong in relation to lower cardiovascular mortality, a key cause of early death in Canadians with COPD.**

It should also be noted that LABA-LAMA-ICS might be prescribed on different inhalers. There is sound evidence, however, that the administration on a single inhaled is associated with decreased healthcare resource utilization and improved cost-effectiveness compared with multiple inhalers (*Zhang et al. Impact of Single Combination Inhaler versus Multiple Inhalers to Deliver the Same Medications for Patients with Asthma or COPD: A Systematic Literature Review COPD; Int J Chron Obstruct Pulmon Dis 2020 Feb 26;15:417-438*). The use of a single device likely improves the deposition of the bronchodilators and steroids on the same location, i.e., the better ventilated alveolar units (*Dunn LR, et al. Pharmacokinetics of budesonide/glycopyrrolate/formoterol fumarate metered dose inhaler formulated using co-suspension delivery technology after single and chronic dosing in patients with COPD. Pulm Pharmacol Ther . 2020 Feb;60:101873. doi: 10.1016/j.pupt.2019.101873.)*

8. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

No: this submission was based on freely-available information (PUBMED) and the physicians' research and clinical experience with the disease.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for <u>each clinician</u> that contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Clinician Information	
Name	*J ALBERTO NEDER, MD, PhD, FRCP(C), FERS*

Position	*Professor, Division of Respirology, Queen's University*
Date	*17-02-2021*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
AstraZeneca	☒	☐	☐	☐
Boehringer Ingelhein	☒	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	*JUAN PABLO DE TORRES, MD, FRCP(C)*
Position	*Professor, Division of Respirology, Queen's University*
Date	*17-02-2021*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
AstraZeneca	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 3

Clinician Information	
Name	*ELIZABETH HILL*
Position	*SPECIALIST (COPD) NURSE PRACTITIONER*
Date	*16-02-2021*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	**Check Appropriate Dollar Range**

	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐