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Reimbursement Recommendation

Beclomethasone, Glycopyrronium, and Formoterol (Trimbow)

Indication: In adult patients who are not adequately treated by a combination of an ICS and a LABA or a combination of a LABA and a LAMA:

- for the long-term, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema
- to reduce exacerbations of COPD in patients with a history of exacerbations.

Sponsor: Methapharm Inc.

Recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Trimbow?

Canada's Drug Agency (CDA-AMC) recommends that Trimbow be reimbursed by public drug plans for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, and to reduce exacerbations (flare-ups) of COPD in patients with a history of flare-ups, if certain conditions are met.

Why Did CDA-AMC Recommend Reimbursement?

The subcommittee of the Canadian Drug Expert Committee (CDEC) determined that Trimbow demonstrates acceptable clinical value versus multiple inhaler triple therapies and single inhaler triple therapies in patients with COPD whose condition is not adequately controlled with optimal dual inhaled therapy. This determination was enough for the subcommittee to recommend that Trimbow be reimbursed.

Evidence from 2 clinical trials showed that outcomes in flare-ups, lung function, health-related quality of life (HRQoL), and adverse effects were similar between Trimbow and 2 multiple inhaler triple therapies (beclomethasone dipropionate–formoterol fumarate plus tiotropium [BDP-FOR + TIO] and fluticasone furoate–vilanterol plus tiotropium [FF-VI + TIO]) in patients with COPD whose condition is not adequately controlled with dual inhaled therapy.

Evidence from an indirect treatment comparison suggested that outcomes in flare-ups and lung function were similar between Trimbow and 2 other single inhaler triple therapies (fluticasone furoate–umeclidinium–vilanterol [FF-UMEC-VI] and budesonide–glycopyrronium–formoterol fumarate [BUD-GLY-FOR]). The indirect treatment comparison did not assess HRQoL or general adverse effects.

Which Patients Are Eligible for Coverage?

Trimbow should only be covered for patients with COPD whose condition is not adequately controlled with optimal dual inhaled therapy.

What Are the Conditions for Reimbursement?

Trimbow should only be reimbursed similarly to currently reimbursed single inhaler triple combination therapies for the same indication. The cost of Trimbow should not exceed that of the least costly single inhaler triple therapy reimbursed for COPD.

Review Background

- **Disease background:** COPD is a chronic lung disease associated with inflammation and obstruction of the airways. COPD progresses through 4 stages of increasing airflow limitation — mild, moderate, severe, and very severe — with symptoms and functional limitations worsening at each stage. Symptoms include difficulty in breathing, cough, and flare-ups (exacerbations) that may require hospitalization. As of 2022 to 2023, the prevalence of COPD was 8.74% in Canada.
- **Indication and reimbursement request:** Beclomethasone dipropionate–glycopyrronium (as bromide)–formoterol fumarate dihydrate (BDP-GLY-FOR) (Trimbow) has been approved by Health Canada for adult patients who are not adequately treated by a combination of an inhaled corticosteroid (ICS) and a long-acting beta$_2$-agonist (LABA) or a combination of a LABA and a long-acting muscarinic antagonist (LAMA):
  - for the long-term, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema
  - to reduce exacerbations of COPD in patients with a history of exacerbations.
- The sponsor is seeking alignment with existing reimbursement criteria for relevant comparator treatments that CDA-AMC has recommended for reimbursement and/or those currently used for the most appropriate comparison treatments (single inhaler triple therapy).
- **Drug under review:** BDP-GLY-FOR is a combination of an ICS, a LAMA, and a LABA. It is administered by oral inhalation, and the dosage recommended in the product monograph is 2 inhalations twice daily.
- **Treatment costs:** At the submitted price of $109.00 per 120-dose inhaler, the annual cost of BDP-GLY-FOR is expected to be $1,327 per patient, based on the Health Canada–recommended dosage.
- **Tailored review process:** This application was reviewed through the tailored review process. When submitting an application for a tailored review, the sponsor does not claim added clinical benefit with the drug under review compared with the most appropriate comparators, and the sponsor requests alignment in the recommendation with existing reimbursement criteria for the most appropriate comparators. A subcommittee of the relevant expert committee deliberates on and, when there is unanimous agreement, issues the recommendation for tailored review applications. The focus of the subcommittee deliberations is whether the evidence shows that the drug under review demonstrates comparable clinical benefit and harms to 1 or more appropriate comparators, and whether the evidence supports the drug being reimbursed in accordance with the existing reimbursement criteria for the most appropriate comparators.

Highlights of Input From Interested Parties

Calls for patient group and clinician group input are issued for every reimbursement review, and submissions received are considered throughout the review. However, for this review, no input was submitted by either patient groups or clinician groups.

The clinical experts consulted by CDA-AMC noted the following regarding unmet needs arising from COPD and the place in therapy for BDP-GLY-FOR:

- **Unmet needs:** a curative therapy, improved disease control, and minimized adverse events.
- **Anticipated place in therapy:** an additional treatment option alongside current triple therapies for patients with COPD who have disease that is not adequately treated by dual therapies or multiple inhaler triple therapies.

The participating public drug programs raised potential implementation issues regarding the initiation, renewal, discontinuation, and prescribing of therapy; the generalizability of trial populations to broader populations; and system and economic issues.

Recommendation

The CDEC subcommittee recommends that BDP-GLY-FOR be reimbursed, only if the conditions listed in Table 1 are met, in adult patients who are not adequately treated by a combination of an ICS and a LABA or a combination of a LABA and a LAMA:

- for the long-term, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema
- to reduce exacerbations of COPD in patients with a history of exacerbations.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation, renewal, discontinuation, and prescribing		
1. Eligibility for reimbursement of BDP-GLY-FOR should align with the criteria used by each of the public drug plans for initiating, renewing, prescribing, and discontinuing single inhaler triple combination formulations currently reimbursed for the same indication.	There is no evidence to suggest that BDP-GLY-FOR should be subject to different requirements than other reimbursed single inhaler triple therapy products for the same indication with respect to initiation, renewal, discontinuation, or prescribing.	The recommendations from Therapeutic Review TR0016 for COPD may also apply to BDP-GLY-FOR, as determined appropriate by the committee responsible for issuing the therapeutic review recommendations.
Pricing		
2. The drug program cost of BDP-GLY-FOR should be negotiated so that it does not exceed the drug program cost of treatment with the least costly single inhaler triple therapy reimbursed for the same indication.	Based on the subcommittee's assessment of the evidence, BDP-GLY-FOR is expected to have comparable or similar clinical benefits and harms compared with relevant comparators. Therefore, the drug program cost of BDP-GLY-FOR should be no more than the least costly single inhaler triple therapy reimbursed for the treatment of COPD.	—

BDP-GLY-FOR = beclomethasone dipropionate–glycopyrronium (as bromide)–formoterol fumarate dihydrate; COPD = chronic obstructive pulmonary disease.

Rationale for the Recommendation

Clinical Value

Evidence from 1 phase III double-blind noninferiority randomized controlled trial (RCT) (TRINITY) and a phase III open-label noninferiority RCT (TRISTAR) showed that 52-week and 26-week treatment with BDP-GLY-FOR, respectively, provided comparable clinical benefit to BDP-FOR + TIO and to FF-VI + TIO in patients with severe or very severe COPD inadequately controlled on dual therapy. Across both trials, BDP-GLY-FOR demonstrated similar outcomes in moderate and severe COPD exacerbation rates, lung function (FEV_1), and HRQoL. The subcommittee deliberated on whether the evidence shows that BDP-GLY-FOR demonstrates comparable clinical benefit and harms to 1 or more appropriate comparators in patients with COPD whose disease is not adequately treated by a combination of an ICS and a LABA or a combination of a LABA and a LAMA. Based on the totality of the clinical evidence, the subcommittee concluded that BDP-GLY-FOR demonstrates comparable clinical benefit and harms compared with multiple inhaler triple therapies and single inhaler triple therapies and therefore has acceptable clinical value.

Evidence of moderate certainty from the TRINITY trial showed that, compared with BDP-FOR + TIO, treatment with BDP-GLY-FOR likely results in little to no difference in the rate of moderate and severe COPD exacerbations and in lung function. Evidence of very low certainty from the TRISTAR trial showed that, compared with FF-VI + TIO, treatment with BDP-GLY-FOR may result in little to no difference in these outcomes. Evidence of low and very low certainty from the 2 trials suggested that treatment with BDP-GLY-FOR may result in little to no difference in HRQoL compared to BDP-FOR + TIO or FF-VI + TIO, respectively. Across the comparisons of BDP-GLY-FOR with BDP-FOR + TIO and with FF-VI + TIO, differences in adverse events were small. There was no evidence for long-term harms beyond the 52-week data reported in the TRINITY trial.

Evidence from sponsor-submitted network meta-analyses (NMAs) suggested similar effects in moderate and severe exacerbation rates or lung function between BDP-GLY-FOR and FF-UMEC-VI, and little to no difference in exacerbation rates between BDP-GLY-FOR and BUD-GLY-FOR. No data were available for lung function for the BUD-GLY-FOR comparison, and the NMAs did not evaluate HRQoL or standard harms.

Further information on the subcommittee's discussion around clinical value is provided in the Summary of Deliberation section.

Developing the Recommendation

The determination of acceptable clinical value was sufficient for the subcommittee to recommend reimbursement of BDP-GLY-FOR.

Because the subcommittee recommended that BDP-GLY-FOR be reimbursed, it also considered whether any reimbursement conditions were needed to address important economic considerations, health system impacts, or social and ethical considerations, or to ensure that clinical value is realized. The resulting reimbursement conditions, with accompanying reasons and implementation guidance, are stated in Table 1.

Summary of Deliberation

The subcommittee considered all domains of value of the deliberative framework before developing its recommendation: clinical value, unmet clinical need, distinct social and ethical considerations, economic considerations, and impacts on health systems. For further information on the domains of value, refer to Expert Committee Deliberation at Canada's Drug Agency.

The subcommittee considered the following key discussion points, organized by the 5 domains of value.

Clinical Value

- **Appropriate comparators:** The most appropriate comparators for the drug under review were single inhaler triple therapies available in Canada, specifically FF-UMEC-VI and BUD-GLY-FOR. Other relevant comparators included multiple inhaler triple therapies, such as BDP-FOR + TIO and FF-VI + TIO.
- **Efficacy of BDP-GLY-FOR versus BDP-FOR + TIO:** One phase III double-blind noninferiority RCT (the TRINITY trial; N = 2,691) demonstrated that treatment with BDP-GLY-FOR for up to 52 weeks likely results in little to no difference in moderate and severe COPD exacerbation rate (absolute mean difference = 0.006; 95% confidence interval [CI], –0.076 to 0.088) and lung function assessed by FEV_1 (adjusted mean difference = –0.003 L; 95% CI, –0.033 L to 0.027 L), compared with BDP-FOR + TIO. The TRINITY trial also suggested that treatment with BDP-GLY-FOR for up to 52 weeks may result in little to no difference in HRQoL assessed by Saint George's Respiratory Questionnaire (SGRQ) (adjusted mean difference = 1.57; 95% CI, 0.10 to 3.05), compared with BDP-FOR + TIO. Certainty of the evidence was rated down for risk of bias and indirectness.
- **Efficacy of BDP-GLY-FOR versus FF-VI + TIO:** One phase III open-label noninferiority RCT (the TRISTAR trial; N = 1,157) suggested that treatment with BDP-GLY-FOR for up to 26 weeks may result in little to no difference in moderate and severe COPD exacerbation rate (absolute mean difference = [redacted]), lung function assessed by FEV_1 (adjusted mean difference = [redacted]), and HRQoL assessed by SGRQ (adjusted mean difference = [redacted]), compared with FF-VI + TIO. However, the evidence is very uncertain due to risk of bias, indirectness, and imprecision.
- **Clinical importance of treatment effects:** The subcommittee considered the treatment effects to be clinically meaningful, given that moderate and severe exacerbation rate, pulmonary function assessed by FEV_1, and HRQoL assessed by SGRQ are important to patients, well-documented in the literature, and used in practice to assess treatment response.
- **Efficacy of BDP-GLY-FOR versus FF-UMEC-VI and BUD-GLY-FOR:** Overall, the available indirect evidence showed that BDP-GLY-FOR may have similar beneficial effects to FF-UMEC-VI and BUD-GLY-FOR, which are the current most appropriate single inhaler triple therapies for comparison. However, the NMA evidence was very uncertain due to wide credible intervals, heterogeneity

across the included studies, and sparse evidence networks. The NMA did not evaluate HRQoL or standard harms.

- **Comparative harms:** Across the comparisons of BDP-GLY-FOR with BDP-FOR + TIO and with FF-VI + TIO, differences in adverse events were small. There was no long-term extension period to assess long-term harms, and follow-up was limited to 1 week after the 26-week treatment period in the TRISTAR trial. The clinical experts consulted by CDA-AMC for this review noted that differences between groups are unlikely, given that the same drug classes were compared; the subcommittee agreed.
- **Clinical value:** Based on the preceding considerations, the subcommittee determined there was comparable or similar clinical value versus appropriate comparators (multiple inhaler triple therapies and single inhaler triple therapies).

Unmet Clinical Need

- **Input on unmet clinical need:** Clinical experts consulted by CDA-AMC for this review identified the following unmet clinical needs: a curative therapy, improved disease control, and minimized adverse events.
- **Deliberation on significant unmet clinical need:** The subcommittee reviewed the considerations for unmet clinical need. Given that deliberations for tailored reviews have a specific focus, further deliberation on whether there was significant unmet clinical need was not required.

Distinct Social and Ethical Considerations

- **Input on unmet nonclinical need:** Clinical experts consulted by CDA-AMC for this review noted that BDP-GLY-FOR is administered twice daily, whereas other single inhaler triple therapies are administered once daily. Clinical experts noted that although this presents a minor additional burden for patients using BDP-GLY-FOR (or for caregivers involved in monitoring or administering treatment), it may still have a meaningful impact on treatment adherence in some patients. The subcommittee further noted that it may have a meaningful impact on treatment adherence compared with multiple inhaler triple therapies but noted the lack of evidence to support this.
- **Deliberation on significant nonclinical need or health inequity:** The subcommittee reviewed the considerations for unmet nonclinical need and health inequity. Given that deliberations for tailored reviews have a specific focus, further deliberation on whether the drug under review addresses a significant unmet nonclinical need or health inequity was not required.

Economic Considerations

- **Cost of BDP-GLY-FOR versus relevant comparators:** Based on the publicly available list prices of all comparators and the sponsor's submitted price of BDP-GLY-FOR, reimbursement of BDP-GLY-FOR is expected to be associated with lower drug costs to the health care system versus other single

inhaler triple therapies (incremental savings = $219 to $349 per year) and with lower or higher costs versus multiple inhaler triple therapies, depending on the combination (range: incremental savings of $1,573 to incremental cost of $404 per year).

- **Other considerations:** In instances in which BDP-GLY-FOR replaces triple therapy regimens consisting of 2 or 3 inhalers, a savings in associated dispensing fees is also expected.

Impacts on Health Systems

- **Anticipated budget impact:** CDA-AMC estimates that the budget impact of reimbursing BDP-GLY-FOR for the indicated population will be a savings of approximately $723,000 over the first 3 years of reimbursement compared to the amount currently spent on its comparators, with an estimated expenditure of $24.6 million on BDP-GLY-FOR over this period. The actual budget impact of reimbursing BDP-GLY-FOR will depend on the number of patients who will receive it, the comparators it will displace, and the confidentially negotiated prices of those comparators.

Sources of Information Used by the Subcommittee

To make its recommendation, the subcommittee considered the following information (links to the full documents for the review can be found on the project web page):

- the CDA-AMC review of the clinical and pharmacoeconomic evidence submitted by the sponsor, related to BDP-GLY-FOR (refer to the main report and the Supplemental Material document)
- the sponsor's comments on the draft report and the CDA-AMC responses
- input from public drug programs that participate in the reimbursement review process (refer to the Supplemental Material document)
- input from 2 clinical experts with expertise in the management of COPD, consulted by CDA-AMC.

CDEC Information

Members of the Committee

Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice-Chair), Sally Bean, Daryl Bell, Dan Dunsky, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Dr. Dennis Ko, Dr. Christine Leong, Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Carla Velastegui, Dr. Edward Xie, and Dr. Peter Zed.

A subcommittee composed of 5 CDEC members was convened. None had a conflict of interest that precluded their participation.

Meeting date: March 10, 2026

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