5.01 BUDESONIDE with GLYCOPYRRONIUM and FORMOTEROL, pressurised inhalation containing budesonide 160 micrograms with glycopyrronium 7.2 micrograms (as bromide) and formoterol fumarate dihydrate 5 micrograms per dose, 120 doses, Breztri Aerosphere®, AstraZeneca Pty Ltd

1 Purpose of Application

1.1 The Category 2 submission requested Authority Required (Streamlined) PBS listing of Breztri Aerosphere®, pressurised metered dose inhaler (pMDI), for the treatment of patients with chronic obstructive pulmonary disease (COPD). Breztri Aerosphere is a triple therapy fixed dose combination (FDC) inhaler comprising an inhaled corticosteroid (ICS), a long acting muscarinic antagonist (LAMA) and a long acting beta-2 agonist (LABA): budesonide (BUD) 160 mcg, glycopyrronium (GLY) (as bromide) 7.2 mcg, and formoterol fumarate dihydrate (FOR) 5 mcg, respectively.

1.2 The basis for the requested listing was a cost-minimisation analysis to Trelegy Ellipta® dry powder inhaler (DPI), which is also a triple therapy FDC inhaler comprising of an ICS/LAMA/LABA: fluticasone furoate (FF) 100 mcg with umeclidinium (UMEC) 62.5 mcg and vilanterol trifenatate (VI) 25 mcg, respectively. FF/UMEC/VI is the only triple therapy FDC inhaler currently listed on the PBS for COPD. In November 2020, the PBAC recommended PBS listing of another triple therapy FDC for COPD, Trimbow® pMDI comprising of beclometasone (BEC) 100 mcg, GLY (as bromide) 10 mcg and FOR 6 mcg. At the time of the submission, BEC/GLY/FOR was not available on the PBS. The submission nominated BEC/GLY/FOR as a near-market comparator.

1.3 Hence, if listed, BUD/GLY/FOR would become the second triple therapy FDC inhaler available on the PBS for COPD after FF/UMEC/VI, or potentially one of three alternatives including BEC/GLY/FOR. The ESC noted that BEC/GLY/FOR was PBS listed for COPD on 1 June 2021.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with moderate to severe COPD and frequent exacerbations despite maintenance therapy.
Intervention	Breztri Aerosphere pMDI, a triple therapy ICS/LAMA/LABA FDC inhaler comprising of BUD 160 mcg / GLY 7.2 mcg / FOR 5 mcg per actuation; two inhalations twice daily.
Comparator	Main comparator: Trelegy Ellipta DPI, a triple therapy ICS/LAMA/LABA FDC inhaler comprising of FF 100 mcg / UMEC 62.5 mcg / VI 25 mcg per actuation; one inhalation once daily. Near market comparator: Trimbow pMDI, a triple therapy ICS/LAMA/LABA FDC inhaler comprising of BEC 100 mcg / GLY 10 mcg / FOR 6 mcg per actuation; two inhalations twice daily.
Outcomes	• Frequency of moderate or severe exacerbations • Change in lung function (FEV1) • Change in quality of life (SGRQ) • Change in use of rescue medications • All-cause mortality and safety
Clinical claim	BUD/GLY/FOR (160/7.2/5) one inhalation once daily is non-inferior (as effective) compared to FF/UMEC/VI (100/62.5/25) one inhalation once daily and BEC/GLY/FOR (100/10/6) two inhalations twice daily, at reducing the risk of moderate to severe exacerbations, improving lung function and comparable in terms of safety.

Abbreviations: BUD=budesonide; COPD=chronic obstructive pulmonary disease; DPI=dry powder inhaler; FDC=fixed dose combination; FEV1=forced expiratory volume in one second; FF=fluticasone fumarate; FOR=formoterol fumarate dihydrate; GLY=glycopyrronium; ICS=inhaled corticosteroid; LABA=long acting beta-2 agonist; LAMA=long acting muscarinic antagonist; pMDI=pressurised metered dose inhaler; SGRQ=St George's Respiratory Questionnaire; mcg=microgram; UMEC=umeclidinium; VI=vilanterol trifenatate;
Source: Table 1.1.1, p14 of the submission.

2 Background

Registration status

2.1 **TGA status at time of PBAC advice**: The submission was made under the TGA/PBAC Parallel Process. At the time of the evaluation, TGA documents were not available. While a Pre-Sub-Committee Response was not submitted the sponsor did provide the TGA clinical evaluation report (dated 31 March 2021) and the TGA Delegate's overview (dated 6 May 2021).

2.2 The proposed TGA indication was:

"Maintenance treatment to prevent exacerbations and relieve symptoms in adults with COPD who require treatment with LAMA+LABA+ICS."

The ESC noted that the TGA Delegate's overview indicated the Delegate was inclined to approve registration for a more restrictive indication:

"Maintenance treatment to prevent exacerbations and relieve symptoms in adults with moderate, severe or very severe COPD who require treatment with a combination of an ICS, a LABA, and a LAMA."

The ESC noted the indication proposed by the Delegate was similar to the FF/UMEC/VI registered indication which allows use for maintenance treatment in adults with moderate to severe COPD who require treatment with LAMA+LABA+ICS.

2.3 The clinical evidence presented in the submission included two formulations of BUD/GLY/FOR, containing different doses of ICS: BUD/GLY/FOR (160/7.2/5) two inhalations twice daily and BUD/GLY/FOR (80/7.2/5) two inhalations twice daily. The submission stated that TGA registration and PBS listing was only sought for the higher dose ICS formulation: BUD/GLY/FOR (160/7.2/5). The clinical evidence demonstrated similar efficacy and safety between the two doses but trends favoured the higher dose.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

3.1 The requested listing is shown below.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Dispensed Price for Max. Qty	Available brands
BUDESONIDE + FORMOTEROL (EFORMOTEROL) + GLYCOPYRRONIUM						
budesonide 160 microgram/actuation + glycopyrronium 7.2 microgram/actuation + formoterol (eformoterol) fumarate dehydrate 5 microgram/actuation inhalation, 120 actuations	NEW	1	1	5	$[redacted]	Breztri Aerosphere 160/7.2/5
Category / Program: GENERAL – General Schedule (Code GE)						
Prescriber type: ☒ Medical Practitioners ☒ Nurse practitioners - CTO						
Restriction type: ☒ Authority Required (STREAMLINED) [10167]						
Administrative Advice: **Continuing Therapy Only:** For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.						
Indication: Chronic obstructive pulmonary disease (COPD)						
Treatment Phase: [blank]						
Clinical criteria:						
Patient must have experienced at least one severe COPD exacerbation, which required hospitalisation, or two or more moderate exacerbations in the previous 12 months, with significant symptoms despite regular bronchodilator therapy with a long acting muscarinic antagonist (LAMA) and a long acting beta-2 agonist (LABA) or an inhaled corticosteroid (ICS) and a LABA; or						
Patient must have been stabilised on a combination of a LAMA, LABA and an ICS for this condition						
Administrative Advice: Formal assessment and correction of inhaler technique should be performed in accordance with the COPD-X Plan (available at http://copdx.org.au/); the assessment and adherence to correct technique should be documented in the patient's medical records.						
Administrative Advice: Diagnosis of COPD should include measurement of airflow obstruction using spirometry, with confirmation of post-bronchodilator airflow obstruction.						
Administrative Advice: This product is not PBS-subsidised for the treatment of asthma or the initiation of bronchodilator therapy in COPD.						
Administrative Advice: The treatment must not be used in combination with an ICS/LABA, LABA/LAMA or LAMA, LABA or ICS monotherapy.						
Administrative Advice: A LAMA includes tiotropium, glycopyrronium, aclidinium or umeclidinium.						
Administrative Advice: A LABA includes olodaterol, indacaterol, salmeterol, formoterol or vilanterol.						
Administrative Advice: An ICS includes fluticasone propionate, fluticasone furoate, budesonide, beclometasone or ciclesonide.						

3.2 The sponsor requested an Authority Required (Streamlined) PBS listing of BUD/GLY/FOR for the treatment of COPD. The requested listing, including the restriction and maximum quantity/repeats, was consistent with the current PBS restriction of FF/UMEC/VI.

3.3 The requested price of BUD/GLY/FOR (AEMP: $[redacted], DPMQ: $[redacted]) was based on a cost-minimisation versus FF/UMEC/VI. No special pricing arrangement was proposed.

3.4 The ESC noted the high number of products (as single agents and as combination products) used in the management of airway/breathing conditions (both COPD and asthma) and that this can make it difficult for prescribers to match the desired product with the patient's condition. The ESC noted the Administrative Advice stating that this product is not PBS-subsidised for the treatment of asthma. The ESC also noted that BUD/GLY/FOR contains FOR, a LABA with a rapid onset of action that in the asthma context can be used when required in the relief of symptoms when combined with an ICS. Currently, FOR is the only LABA used in this context. As some patients may have asthma-COPD overlap, the PBAC agreed with the ESC that it would be appropriate to convey in the listing that this product is not indicated as reliever therapy and that the listing is intended to facilitate regular, twice daily dosing as per the approved Product Information. The PBAC noted that PBS restrictions aim to set out the circumstances under which an item is made a PBS benefit and do not intend to provide clinical advice. In addition, the PBAC considered the circumstances of PBS eligibility applicable to all three triple therapy FDCs for COPD should be no different.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 COPD is a progressive and chronic inflammatory lung disease that is characterised by airflow limitation and chronic respiratory symptoms such as dyspnoea (breathlessness), cough and sputum production. The most important risk factors for developing COPD are cigarette smoking and passive exposure to smoking. COPD mostly affects middle aged and older people, and is commonly associated with multiple co-morbidities.

4.2 The clinical course of COPD is defined by periods of stable disease and acute exacerbations, characterised by worsening symptoms and hospitalisations. A history of exacerbation is associated with an increased risk of future exacerbations. The Global Initiative for COPD (GOLD 2021)[1] guidelines classify exacerbations as mild (treated with short acting bronchodilators only), moderate (treated with short-acting bronchodilators plus antibiotics and/or oral corticosteroids) or severe (requiring hospitalisation or emergency room visit). Severe exacerbations may also be associated with acute respiratory failure or result in death.

4.3 The submission proposed that BUD/GLY/FOR would be an alternative triple therapy ICS/LAMA/LABA FDC inhaler to FF/UMEC/VI in patients who have repeated exacerbations and significant symptoms despite LAMA/LABA or ICS/LABA dual therapy or who have been stabilised on an open triple therapy combination of ICS, LAMA and LABA. The proposed population and place in therapy was consistent with the current PBS listing for FF/UMEC/VI and clinical guidelines.

For more detail on PBAC's view, see section 7 PBAC outcome.

[1] Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2021. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Pocket guide to COPD diagnosis, management and prevention.

5 Comparator

5.1 The submission nominated FF/UMEC/VI, one inhalation once daily, as the main comparator because it is the only triple therapy ICS/LAMA/LABA FDC inhaler currently PBS listed for COPD and is the medicine most likely to be replaced by BUD/GLY/FOR. The submission also nominated BEC/GLY/FOR, two inhalations twice daily, as a near market comparator. In November 2020, the PBAC recommended listing of BEC/GLY/FOR for COPD but it was not available on the PBS at the time of the submission.

5.2 The evaluation considered the nominated comparators were appropriate, however in practice, BUD/GLY/FOR would also substitute for other combinations of ICS, LAMA and LABA inhalers. In addition to the individual components of the inhaler (i.e. BUD, GLY and FOR), the PBAC has previously considered that any combination of ICS, LAMA and LABA given concomitantly were relevant comparators for triple therapy FDC inhalers (paragraph 7.4, Trimbow (BEC/GLY/FOR) Public Summary Document (PSD) November 2020 PBAC meeting).

5.3 Based on this principle, there are many potential comparators for BUD/GLY/FOR because there are numerous ICS, LAMA and LABA agents available on the PBS for COPD, either alone or in combination. The individual components of BUD/GLY/FOR are PBS listed for COPD using a combination of inhaler devices: GLY is available as dry powder capsules for inhalation (Seebri Breezhaler®), and BUD/FOR are available as a dual therapy FDC pMDI or DPI (Symbicort Rapihaler® and Symbicort Turbuhaler®, respectively).

5.4 The submission noted that BUD/GLY/FOR (160/7.2/5) is labelled according to the 'delivered dose' per actuation, whereas FF/UMEC/VI (100/62.5/25) and BEC/GLY/FOR (100/10/6) are labelled according to the 'metered dose' per actuation. This difference is due to new TGA labelling requirements, introduced 31 August 2016 and effective from 1 September 2020, which requires the delivered dose to be included on labelling unless the therapeutic dose was clinically established using the metered dose. According to the Australian Commission on Safety and Quality in Health Care[2], the delivered dose is the more accurate measure of the amount of active ingredient reaching the patient and is used to describe the dose of new medicines or new presentations of medicines. However, the regulation allows flexibility for established medicines to continue to be described by the metered dose.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

[2] Australian Commission on Safety and Quality of Health Care, 2019. Safety statement on metered dose inhalers. [https://www.safetyandquality.gov.au/sites/default/files/2019-12/metered_dose_inhalers_safety_statement_2019.pdf]

Consumer comments

6.2 The PBAC noted and welcomed the input from Lung Foundation Australia via the Consumer Comments facility on the PBS website. The comments described having three medicines in one device (BUD/GLY/FOR) as cost effective for patients, environmentally sustainable and may help with taking doses regularly. The comments also indicated clinicians and patients with COPD would appreciate having additional treatment choices for this condition.

Clinical trials

6.3 The submission was based on five randomised controlled trials (ETHOS, KRONOS, IMPACT, TRIBUTE, TRILOGY) comparing triple therapy FDCs (ICS/LAMA/LABA) to dual therapy FDCs (LAMA/LABA and/or ICS/LABA). Four of these trials were used to inform an indirect comparison between BUD/GLY/FOR versus FF/UMEC/VI and BEC/GLY/FOR. The PBAC has previously considered evidence from three of the five included trials (IMPACT, TRIBUTE and TRILOGY).

Table 2: Trials presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Breztri (BUD/GLY/FOR) vs GLY/FOR and BUD/FOR		
ETHOS NCT02465567 JPRN-JapicCTI-184078	A Randomized, Double-Blind, Multi-Center, Parallel-Group Study to Assess the Efficacy and Safety of PT010 Relative to PT003 and PT009 on COPD Exacerbations over a 52-Week Treatment Period in Subjects with Moderate to Very Severe COPD. Rabe KF, et al. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD.	8 November 2019 New England Journal of Medicine 2020; 383(1):35-48
KRONOS NCT02497001 JPRN-JapicCTI-184079 (Extension NCT03262012 JPRN-JapicCTI-184080)	A Randomized, Double-Blind, Parallel-Group, 24-Week, Chronic-Dosing, Multi-Center Study to Assess the Efficacy and Safety of PT010, PT003, and PT009 Compared with Symbicort® Turbuhaler® as an Active Control in Subjects with Moderate to Very Severe Chronic Obstructive Pulmonary Disease. Ferguson GT, et al. Triple therapy with budesonide/ glycopyrrolate/ formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, phase 3 randomised controlled trial.	6 June 2018. The Lancet Respiratory Medicine 2018; 6(10):747-758
Trelegy (FF/UMEC/VI) vs UMEC/VI and FF/VI		
IMPACT	Lipson DA, et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD.	New England Journal of Medicine 2018; 378(18): 1671-1680
Trimbow (BEC/GLY/FOR) vs GLY/IND		
TRIBUTE	Papi A, et al. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial.	The Lancet 2018; 391(10125):1076-1084.
Trimbow (BEC/GLY/FOR) vs BEC/FOR		
TRILOGY	Singh D, et al. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial.	The Lancet 2016; 388:963-973

Abbreviations: BEC=beclometasone dipropionate; BUD=budesonide; COPD=chronic obstructive pulmonary disease; FF=fluticasone furoate; FOR=formoterol fumarate dihydrate; GLY=glycopyrronium; IND=indacaterol; UMEC=umeclidinium; VI=vilanterol trifenatate;
Source: Table 2.2.1 to 2.2.3, pp36-37 of the submission.

6.4 The submission described KRONOS as supportive evidence and did not include results in the indirect treatment comparison, owing to differences in the trial durations/outcomes (24 vs 52 weeks) and population (no enrolment criteria on exacerbations history versus prior history of ≥1 moderate/severe exacerbations). This

was generally reasonable given the majority of patients in KRONOS had not experienced an exacerbation in the past 12 months at baseline, but this was also unlikely to influence results. The submission also reasonably excluded the FULFIL trial comparing FF/UMEC/VI to BUD/FOR as the trial only reported exacerbation rates at 52 weeks for a subgroup with unclear randomisation and baseline characteristics. Data from this subgroup (n=430 patients) was included in the PBAC submission of BEC/GLY/FOR despite the same concern (paragraph 6.10, Trimbow (BEC/GLY/FOR) PSD November 2020 PBAC meeting).

6.5 Data from KRONOS was included in a network meta-analysis by Bourdin et al 2020 (draft manuscript only). The network meta-analysis included data from 15 double-blind RCTs (including ETHOS, KRONOS, IMPACT, TRIBUTE and TRILOGY) and compared BUD/GLY/FOR to FF/UMEC/VI, BEC/GLY/FOR and open combinations of triple therapy for several key outcomes at Week 24 and Week 52. The results from this study demonstrated results at Week 24 (including KRONOS) were comparable to results at Week 52 (excluding KRONOS).

6.6 Table 3 presents the key features of the included trials. ETHOS randomised patients to BUD/GLY/FOR FDCs with different doses of BUD (i.e. 160 or 80 mcg). As the submission only requested TGA registration and PBS listing for the higher dose formulation, BUD/GLY/FOR (160/7.2/5), the evaluation focuses only on results from that treatment arm.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Bias	Treatment arms	Population	Key efficacy outcomes
Breztri (BUD/GLY/FOR) v GLY/FOR and BUD/FOR						
ETHOS	8509	R, MC, DB, parallel, 4w run-in[a] + 52w	Low	BUD/GLY/FOR 160/7.2/5 pMDI* BUD/GLY/FOR 80/7.2/5 pMDI* GLY/FOR 7.2/5 pMDI* BUD/FOR 160/5 pMDI*	Moderate to very severe COPD + history of moderate to severe exacerbations	1°: exacerbation rate other: trough FEV1, SGRQ, rescue drugs
KRONOS	1902	R, MC, DB, parallel, 4w run-in[b] + 24w	Low	BUD/GLY/FOR 160/7.2/5 pMDI* GLY/FOR 7.2/5 pMDI* BUD/FOR 160/5 pMDI* BUD/FOR 200/6 DPI*#	Moderate to very severe COPD	1°: trough FEV1 2°: exacerbation rate, SGRQ, rescue drugs
Trelegy (FF/UMEC/VI) v UMEC/VI and FF/VI						
IMPACT	10355	R, MC, DB, parallel, 2w run-in[c] + 52w	Low	FF/UMEC/VI 100/62.5/25 DPI^ UMEC/VI 62.5/25 DPI^ FF/VI 100/25 DPI^	Moderate to very severe COPD + history of moderate to severe exacerbations	1°: exacerbation rate 2°: trough FEV1, SGRQ
Trimbow (BEC/GLY/FOR) v GLY/IND						
TRIBUTE	1532	R, MC, DB, DD‡, parallel, 2w run-in[d] + 52w	Low	BEC/GLY/FOR 100/12.5/6 pMDI* GLY/IND 50/110 DPI^	Severe to very severe COPD + history of moderate to severe exacerbations	1°: exacerbation rate 2°: trough FEV1, SGRQ, rescue drugs
Trimbow (BEC/GLY/FOR) v BEC/GLY						
TRILOGY	1368	R, MC, DB, parallel, 2w run-in[e] + 52w	Low	BEC/GLY/FOR 100/12.5/6 pMDI* BEC/FOR 100/6 pMDI*	Severe to very severe COPD + history of moderate to severe exacerbations	1°: trough FEV1 2°: exacerbation rate, SGRQ, rescue drugs

Abbreviations: BEC=beclometasone dipropionate; BUD=budesonide; COPD=chronic obstructive pulmonary disease; DB=double-blind; DD=double dummy; DPI=dry powder inhaler; FEV1=forced expiratory volume in one second; FF=fluticasone furoate; FOR=formoterol fumarate dihydrate; GLY=glycopyrronium; IND=indacaterol; MC=multi-centre; pMDI=pressurised metered dose inhaler; R=randomised; SGRQ=St George's Respiratory Questionnaire; UMEC=umeclidinium; VI=vilanterol trifenatate; w=week;

* Administered as 2 inhalations twice daily

^ Administered 1 inhalation once daily

supplied as open label

‡ double-dummy with each patient using both a pMDI (containing BEC/GLY/FF or placebo) and a single-dose DPI (placebo or GLY/IND).

a During screening (4 weeks), all eligible patients discontinued COPD medications (except for ICS if used before screening) or changed COPD medications (i.e. ipratropium bromide during screening and albuterol for rescue use throughout the study). Ipratropium and ICS were discontinued at the time of randomization.

b During screening (4 weeks), all eligible patients discontinued prohibited COPD medications and underwent a washout period. Patients received open-label ipratropium bromide administered four times daily for COPD maintenance. Patients were permitted to use ICS during the screening period providing they had been maintained on a stable dose for 4 weeks prior to screening. Those receiving maintenance dose of ICS as part of FDC with a LABA, discontinued the FDC and switched to the corresponding ICS dose administered as monotherapy.

c During run-in phase (2 weeks), patients continued to take their own medication (including a LAMA, LABA, or an ICS alone or in combination) before randomization.

d During run-in phase (2 weeks), all patients had their COPD maintenance therapy switched to open-label GLY/IND 50/110 DPI one actuation per day.

e During run-in phase (2 weeks), all patients received open label BEC/FOR 100/6 pMDI two actuations twice daily.

Source: compiled from Section 2.3, pp41-48 of the submission, Rabe et al 2020, Ferguson et al 2018, Lipson et al 2018, Papi et al 2018 and Singh et al 2016.

6.7 All were multicentre, double blind, randomised, parallel group trials investigating the efficacy and safety of triple therapy FDCs versus dual therapy FDCs (ICS/LABA and/or LAMA/LABA). The duration of the double-blind phases were 52 weeks except for KRONOS (24 weeks), and all trials reported moderate to severe exacerbations rates and FEV1 as primary or secondary outcomes. Overall, the risk of bias within the trials was low.

6.8 There were, however, a number of differences across the trials in terms of study design and selection criteria. For example, each trial had a run-in/screening period, ranging from two to four weeks, during which maintenance COPD medications (i.e.

LAMA, LABA and ICS) were either i) discontinued, ii) continued or iii) changed to the same treatments. The trials used slightly different diagnostic/classification criteria for severity of disease, and had different requirements in terms of the number of exacerbations in the past 12 months and prior COPD maintenance treatments.

6.9 Patient characteristics were generally similar between treatment arms, however, there were differences across the trials owing in part to differences in the selection criteria, particularly in terms of:

- The number of moderate/severe exacerbations in past 12 months (fewer in KRONOS, TRIBUTE and TRILOGY compared to the other trials),
- COPD maintenance therapy at screening (mostly dual therapy in TRIBUTE and TRILOGY, compared to mostly dual or triple therapy in the other trials),
- Post-bronchodilator FEV1% (% of predicted FEV1) at baseline (lower in TRIBUTE and TRILOGY compared to the other trials).

6.10 The submission argued that any differences in patient characteristics across the trials were unlikely to bias the results of the indirect comparison (i.e. impact the transitivity assumption), given the treatments effects within trials were generally comparable. Overall, the evaluation considered this was probably reasonable. Despite differences across a number of important characteristics, the trial results demonstrated similar treatment effects over key subgroups (including prior exacerbations, prior COPD medications, and lung function at baseline). In addition, Bourdin et al 2020 found consistent results in terms of the rate of exacerbation after adjusting for differences in important treatment effect modifiers using meta-regression.

6.11 The PBAC has previously considered lung function (i.e. FEV1), frequency of exacerbations and hospitalisations as being patient relevant outcomes in COPD (paragraph 6.8, fluticasone vilanterol PSD March 2014 PBAC meeting). In determining non-inferiority between triple therapy FDC inhalers, the PBAC has also considered evidence across other outcomes including quality of life (the St George's Respiratory Questionnaire, SGRQ) and the use of rescue medication (paragraph 6.8, Trelegy (FF/UMEC/VI) PSD December 2017 PBAC meeting).

6.12 The submission presented a series of pairwise indirect treatment comparisons comparing BUD/GLY/FOR to FF/UMEC/VI and BEC/GLY/FOR across these outcomes, reported at Week 52 in the trials (rate of moderate or severe exacerbations, change in morning pre-dose trough FEV1, change in SGRQ, and change in use of daily rescue medication). The indirect treatment comparisons used either ICS/LABA or LAMA/LABA FDC inhalers as the common reference, based on the assumption that different agents from the same class have comparable efficacy and safety. This assumption was reasonable and consistent with past decisions, where the PBAC has considered "medicines in the LAMA, LABA, ICS/LABA and LAMA/LABA classes to be of comparable efficacy and similar safety to other medicines within their class" (Attachment 1A, Post-market Review of COPD Medicines July 2017).

6.13 The submission stated there is no widely accepted minimal clinically important difference (MCID) for the rate of exacerbations. For other outcomes, an increase in trough FEV1 of 100 mL and a decrease in SGRQ of 4-points are considered to be clinically relevant. A literature review of the MCID for exacerbations by Chapman et al

2013[3] suggests that reduction in the annual rate of exacerbations of 11% may be clinically important, but interpretation requires consideration of the baseline rate and exacerbation severity (as well as the duration of the trial). This review noted that the estimate of 11% was less than the previously 'established' MCID of 20% in Calverley et al 2005.

6.14 The submission did not nominate a non-inferiority margin for any of the outcomes, and assessed non-inferiority between the triple therapy FDC inhalers based on a lack of statistical significance in the rate of moderate or severe exacerbations. In the November 2020 submission of BEC/GLY/FOR the ESC noted that the lack of a statistically significant difference between treatments is not a robust method for determining non-inferiority and may not adequately justify a claim of similar efficacy (paragraph 6.29, Trimbow (BEC/GLY/FOR) PSD November 2020 PBAC meeting).

Comparative effectiveness

6.15 Table 4 presents the results from the included trials at Week 52, as well as the results of the indirect comparisons between BUD/GLY/FOR versus FF/UMEC/VI and BEC/GLY/FOR.

[3] Chapman KR, Bergeron C, Bhutani M, Bourbeau J, Grossman RF, Hernandez P, McIvor RA, Mayers I. 2013. Do We Know the Minimal Clinically Important Difference (MCID) for COPD Exacerbations?, COPD: Journal of Chronic Obstructive Pulmonary Disease, 10(2):243-249.

Table 4: Key efficacy outcomes reported in the ITT at 52 weeks

Trial	ICS/LAMA/LABA	ICS/LABA	LAMA/LABA	Treatment difference (95%CI) ICS/LABA/LAMA vs ICS/LABA	Treatment difference (95%CI) ICS/LABA/LAMA vs LAMA/LABA
Moderate or severe exacerbations, annual rate				**RR**	**RR**
	BUD/GLY/FOR	BUD/FOR	GLY/FOR		
ETHOS[a]	1.08 *(1.00, 1.16)*	1.24 *(1.16, 1.32)*	1.42 *(1.32, 1.52)*	**0.87 (0.79, 0.95)**	**0.76 (0.69, 0.83)**
	FF/UMEC/VI	FF/VI	UMEC/VI		
IMPACT[b]	0.91 (0.87, 0.95)	1.07 (1.02, 1.12)	1.21 (1.14, 1.29)	**0.85 (0.80, 0.90)**	**0.75 (0.70, 0.81)**
	BEC/GLY/FOR	BEC/FOR	GLY/IND		
TRILOGY[c]	0.41 (0.36, 0.47)	0.53 (0.47, 0.60)	-	**0.77 (0.65, 0.92)**	-
TRIBUTE[d]	0.50 (0.45, 0.57)	-	0.59 (0.53, 0.67)	-	**0.85 (0.72, 0.995)**
Morning pre-dose trough FEV_1 (mL), LS mean change from baseline				**MD**	**MD**
	BUD/GLY/FOR	BUD/FOR	GLY/FOR		
ETHOS	119 (107, 132)	47 (34, *60*)	74 (61, 87)	**72 (54, 90)**	**46 (27, 64)**
ETHOS‡	99 (82, 116)	34 (17, 52)	44 (27, 62)	**65 (40, 89)**	**55 (30, 79)**
	FF/UMEC/VI	FF/VI	UMEC/VI		
IMPACT	94 (86, 102)	-3 (-12, 6)	40 (28, 52)	**97 (85, 109)**	**54 (39, 69)**
	BEC/GLY/FOR	BEC/FOR	GLY/IND		
TRILOGY	71 (50, 93)	8 (-14, 30)	-	**63 (32, 94)**	-
TRIBUTE	-29 (-46, 12)	-	-49 (-66, -31)	-	19 (-5, 43)
SGRQ score, LS mean change from baseline				**MD**	**MD**
	BUD/GLY/FOR	BUD/FOR	GLY/FOR		
ETHOS	-6.4 (-6.9, -5.9)	-5.1 (-5.6, -4.6)	-4.8 (-5.3, -4.3)	**-1.3 (-2.0, -0.6)**	**-1.6 (-2.3, -0.9)**
ETHOS‡	-6.4 (-7.0, -5.7)	-4.9 (-5.6, -4.2)	-4.5 (-5.2, -3.8)	**-1.5 (-2.4, -0.5)**	**-1.9 (-2.8, -0.9)**
	FF/UMEC/VI	FF/VI	UMEC/VI		
IMPACT	-5.5 (-5.9, 5.0)	-3.7 (-4.2, -3.2)	-3.7 (-4.4, 3.0)	**-1.8 (-2.4, -1.1)**	**-1.8 (-2.6, -1.0)**
	BEC/GLY/FOR	BEC/FOR	GLY/IND		
TRILOGY#	-5.1 (-6.2, -4.1)	-3.4 (-4.5, -2.4)	-	**-1.7 (-3.2, -0.17)**	-
TRIBUTE	-3.5 (-4.4, -2.6)	-	-1.8 (-2.7, -1.0)	-	**-1.6 (-2.9, -0.4)**
Daily puffs of rescue medication, LS mean change from baseline				**MD**	**MD**
	BUD/GLY/FOR	BUD/FOR	GLY/FOR		
ETHOS	-0.6 (-0.7, -0.5)	-0.3 (-0.4, -0.2)	-0.2 (-0.3, -0.1)	**-0.30 (-0.43, -0.17)**	**-0.41 (-0.54, -0.28)**
ETHOS‡	-0.6 (-0.7, -0.5)	-0.3 (-0.5, -0.2)	-0.1 (-0.2, 0)	**-0.25 (-0.41, -0.09)**	**-0.49 (-0.65, -0.32)**
	BEC/GLY/FOR	BEC/FOR	GLY/IND		
TRILOGY	-0.04 (-0.17, 0.09)	0.07 (-0.07, 0.21)	-	-0.11 (-0.30, 0.08)	-
TRIBUTE^	-0.29 (-0.41, -0.16)	-	-0·25 (-0.37, -0.12)	-	-0.04 (-0.22, 0.14)

Indirect comparisons	Common comparator ICS/LABA	Common comparator LAMA/LABA
Outcome: Moderate or severe exacerbations rate	**RR**	**RR**
BUD/GLY/FOR vs FF/UMEC/VI	1.02 (0.91, 1.15)	1.01 (0.90, 1.14)
BUD/GLY/FOR vs BEC/GLY/FOR	1.13 (0.93, 1.37)	0.90 (0.74, 1.08)
Outcome: Morning pre-dose trough FEV_1 (mL)	**MD**	**MD**
BUD/GLY/FOR vs FF/UMEC/VI	**-25 (-47, -3)**	-8 (-31, 15)
BUD/GLY/FOR vs BEC/GLY/FOR	9 (-27, 45)	27 (-3, 57)
BUD/GLY/FOR‡ vs FF/UMEC/VI	**-32 (-59, -5)**	1 (-28, 30)
BUD/GLY/FOR‡ vs BEC/GLY/FOR	2 (-38, 42)	36 (2, 70)
Outcome: SGRQ score	**MD**	**MD**
BUD/GLY/FOR vs FF/UMEC/VI	0.49, (-0.41, 1.39)	0.21 (-0.84, 1.26)
BUD/GLY/FOR vs BEC/GLY/FOR	0.38, (-1.27, 2.03)	0.05 (-1.36, 1.46)
BUD/GLY/FOR‡ vs FF/UMEC/VI	0.33 (-0.83, 1.49)	-0.08 (-1.33, 1.17)
BUD/GLY/FOR‡ vs BEC/GLY/FOR	0.22 (-1.57, 2.01)	-0.24 (-1.81, 1.33)
Outcome: Daily puffs of rescue medication	**MD**	**MD**
BUD/GLY/FOR vs BEC/GLY/FOR	-0.19, (-0.42, 0.04)	**-0.37, (-0.59, -0.15)**
BUD/GLY/FOR‡ vs BEC/GLY/FOR	-0.14 (-0.39, 0.11)	**-0.45 (-0.69, -0.21)**

Abbreviations: BEC=beclometasone dipropionate; BUD=budesonide; FF=fluticasone fumarate; FOR=formoterol fumarate dihydrate; CI=confidence interval; FEV1=forced expiratory volume in 1 second; GLY=glycopyrronium; ICS=inhaled corticosteroids; IND=indacaterol; ITT=intention to treat; LABA=long acting beta-2 agonist; LAMA=long acting muscarinic antagonist; LS=least square; MD=mean difference; RR=rate ratio; SQRQ-C=St. George's Respiratory Questionnaire COPD; UMEC=umeclidinium; VI=vilanterol trifenatate;

a Treatments were compared adjusting for baseline post-bronchodilator percent predicted FEV1, baseline COPD exacerbation history (1/≥2), log baseline blood eosinophil count, region, and ICS use at screening (yes/no) using negative binomial regression. The logarithm of the time at risk of experiencing an exacerbation was used as an offset variable in the model.
b Generalised linear model assuming a negative binomial distribution and covariates of treatment group, gender, exacerbation history (≤1, ≥2 moderate/severe), smoking status (Screening), geographic region, post-bronchodilator percent predicted FEV1 (Screening).
c Analysis used negative binomial model that included treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation, smoking status at screening, and the baseline value (where available) were included as fixed effects, and log-time in the study as an offset.
d Analysis used negative binomial model that included treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation, and smoking status as fixed effects, and log-time in the study as an offset.
‡ The evaluation presented results of the mean change from baseline at Week 52, consistent with results presented for other trials. The submission presented results of the mean change from baseline over 52 weeks.
# Derived from Singh et al 2020 and Table 7, Trimbow (BEC/GLY/FOR) PSD November 2020 PBAC meeting.
^ revised during the evaluation to adjusted mean change from baseline at Weeks 41-52 (supplementary Table 1, Papi et al 2018). The submission presented the results by treatment arms over 52 weeks but the mean difference was based on results at Weeks 41-52.
Source: Table 2.5.1, pp66-67, Tables 2.5.3 to 2.5.5, pp69-72, Table 2.6.1, p82 and Table 2.6.3, p85 of the submission.

6.16 The trial results demonstrated that each of the triple therapy ICS/LAMA/LABA FDCs was more effective than dual therapy ICS/LABA and LAMA/LABA FDCs in reducing the annual rate of moderate or severe exacerbations, pre-dose trough FEV1, reduction in daily rescue medication and SGRQ score at Week 52. The findings were consistent with numerical trends reported in KRONOS at Week 24, however, only the treatment difference in pre-dose trough FEV1 was statistically significant.

6.17 Based on the indirect treatment comparisons, BUD/GLY/FOR, FF/UMEC/VI and BEC/GLY/FOR had similar efficacy across all of the outcomes considered. Using the ICS/LABA as the common reference, there was a statistically larger improvement in trough FEV1 with FF/UMEC/VI versus BUD/GLY/FOR, but the difference was not clinically important (the difference was less than the MCID of ≥100 mL). Using the LAMA/LABA as the common reference, there was a statistically larger reduction in daily rescue medication use for BUD/GLY/FOR compared to FF/UMEC/VI and BEC/GLY/FOR, but this finding was not supported using an ICS/LABA as the common reference. Non-inferiority between the triple therapy FDCs was concluded because there were no statistically significant differences in terms of the rate of exacerbations.

6.18 Overall, these findings were consistent with the results from the network meta-analysis by Bourdin et al 2020 (draft manuscript), which found that the efficacy of BUD/GLY/FOR was comparable to FF/UMEC/VI and BEC/GLY/FOR and open triple therapy combinations (i.e. ICS/LABA + LAMA) at 24 and 52 weeks.

Comparative harms

6.19 The incidence of AEs for BUD/GLY/FOR was comparable to GLY/FOR and BUD/FOR, at Week 24 in KRONOS and Week 52 in ETHOS. Across the trials, the incidence of any AEs, serious AEs and AEs leading to discontinuations were also comparable between all the triple therapy FDC inhalers and dual therapy FDC inhalers. Commonly reported AEs included nasopharyngitis, COPD, pneumonia and respiratory tract infection. AEs of special interest included pneumonia and major adverse cardiovascular events (MACE).

6.20 Table 5 presents key safety outcomes in the trials at Week 52, and results of indirect comparisons between BUD/GLY/FOR versus FF/UMEC/VI and BEC/GLY/FOR (using ICS/LABA and LAMA/LABA as the common reference). There were no statistically significant differences in safety outcomes for BUD/GLY/FOR, FF/UMEC/VI and BEC/GLY/FOR.

Table 5: Key safety outcomes reported in the ITT at 52 weeks

Trial	ICS/LAMA/LABA	ICS/LABA	LAMA/LABA	Treatment difference (95%CI) ICS/LABA/LAMA vs ICS/LABA	Treatment difference (95%CI) ICS/LABA/LAMA vs LAMA/LABA
All-cause mortality (including off-treatment follow-up), n/N (%)				**HR**	**HR**
	BUD/GLY/FOR	BUD/FOR	GLY/FOR		
ETHOS	28/2137 (1.3)	34/2131 (1.6)	49/2120 (2.3)	0.78 (0.47, 1.30)^	**0.54 (0.34, 0.87)^**
	FF/UMEC/VI	FF/VI	UMEC/VI		
IMPACT	89/4151 (2.1)	97/4134 (2.3)	60/2090 (2.9)	0.90 (0.67, 1.20)	**0.71 (0.51, 0.99)**
Any AEs, n/N (%)				**RR**	**RR**
	BUD/GLY/FOR	BUD/FOR	GLY/FOR		
ETHOS	1368/2144 (64)	1377/2136 (65)	1312/2125 (62)	0.99 (0.95, 1.04)	1.03 (0.99, 1.08)
	FF/UMEC/VI	FF/VI	UMEC/VI		
IMPACT	2897/4151 (70)	2800/4134 (68)	1429/2070 (69)	1.03 (1.00, 1.06)	1.01 (0.98, 1.05)
	BEC/GLY/FOR	BEC/FOR	GLY/IND		
TRILOGY	368 / 687 (54)	379/680 (56)	-	0.96 (0.87, 1.06)	
TRIBUTE	490/764 (64)	-	516 / 768 (67)		0.95 (0.89, 1.03)
Serious AEs, n/N (%)				**RR**	**RR**
	BUD/GLY/FOR	BUD/FOR	GLY/FOR		
ETHOS	426/2144 (20)	440/2136 (21)	433/2125 (20)	0.96 (0.86, 1.09)	0.98 (0.87, 1.10)
	FF/UMEC/VI	FF/VI	UMEC/VI		
IMPACT	895/4151 (22)	850/4134 (21)	470/2070 (23)	1.05 (0.96, 1.14)	0.95 (0.86, 1.05)
	BEC/GLY/FOR	BEC/FOR	GLY/IND		
TRILOGY	106/687 (15)	123/680 (18)	-	0.85 (0.67, 1.08)	
TRIBUTE	117/764 (15)	-	130/768 (17)		0.90 (0.72, 1.14)
Pneumonia, n/N (%)				**RR**	**RR**
	BUD/GLY/FOR	BUD/FOR	GLY/FOR		
ETHOS	98/2144 (5)	107/2136 (5)	61/2125 (3)	0.91 (0.70, 1.19)	1.59 (1.16, 2.18)
	FF/UMEC/VI	FF/VI	UMEC/VI		
IMPACT	317/4151 (8)	292/4134 (7)	97/2070 (5)	1.08 (0.93, 1.26)	1.63 (1.31, 2.03)
	BEC/GLY/FOR	BEC/FOR	GLY/IND		
TRILOGY	23/687 (3)	18/680 (3)	-	1.26 (0.69, 2.32)	
TRIBUTE^	28/764 (4)	-	27/768 (4)		1.04 (0.62, 1.75)

Indirect comparisons	Common comparator ICS/LABA	Common comparator LAMA/LABA
All-cause mortality	**HR**	**HR**
BUD/GLY/FOR vs FF/UMEC/VI	0.87 (0.48, 1.56)	0.76 (0.43, 1.35)
Any AEs	**RR**	**RR**
BUD/GLY/FOR vs FF/UMEC/VI	0.96 (0.91, 1.01)	1.02 (0.96, 1.08)
BUD/GLY/FOR vs BEC/GLY/FOR	1.03 (0.93, 1.15)	1.08 (0.99, 1.18)
Serious AEs	**RR**	**RR**
BUD/GLY/FOR vs FF/UMEC/VI	0.91 (0.79, 1.06)	1.03 (0.88, 1.02)
BUD/GLY/FOR vs BEC/GLY/FOR	1.13 (0.87, 1.47)	1.09 (0.84, 1.41)
Pneumonia	**RR**	**RR**
BUD/GLY/FOR vs FF/UMEC/VI	0.84 (0.62, 1.14)	0.98 (0.66, 1.43)
BUD/GLY/FOR vs BEC/GLY/FOR	0.72 (0.37, 1.40)	1.53 (0.83, 2.81)

Abbreviations: BEC=beclometasone dipropionate; BUD=budesonide; FF=fluticasone fumarate; FOR=formoterol fumarate dihydrate; GLY=glycopyrronium; ICS=inhaled corticosteroids; IND=indacaterol; ITT=intention to treat; LABA=long acting beta-2 agonist; LAMA=long acting muscarinic antagonist; HR=hazard ratio; RR=rate ratio; UMEC=umeclidinium; VI=vilanterol trifenatate;

^ Data included patients missing Week 52 vital status (n=384). The submission reported analysis provided by Martinez et al 2020, which included Week 52 vital status for 99.6% of ITT population, showed the risk of death for Breztri (BUD/GLY/FOR) was significantly lower versus GLY/FOR (HR: 0.51, 95%CI: 0.33, 0.80), but no significant difference versus BUD/FOR (HR: 7.2, 95%CI: 0.44, 1.16).

Source: Table 2.5.2, pp67-68, Tables 2.5.7 to 2.5.8, pp73-74, Table 2.5.12, pp76-77, Table 2.6.1, p82 and Table 2.6.4, p86 of the submission.

Clinical claim

6.21 The submission described BUD/GLY/FOR as non-inferior in terms of comparative efficacy and safety compared to FF/UMEC/VI and BEC/GLY/FOR, for patients with moderate to severe COPD.

6.22 The ESC agreed with the evaluation that overall the clinical claim was supported by the indirect evidence presented in the submission. The claim for non-inferior efficacy was based on comparable reduction in moderate or severe exacerbations and change in lung function (FEV1), SGRQ score and rescue medication use at Week 52; the claim of non-inferior safety was based on comparable incidence of AEs at Week 52.

6.23 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.

6.24 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

6.25 The submission presented a cost-minimisation analysis between BUD/GLY/FOR and FF/UMEC/VI, based on the following equi-effective doses:

BUD/GLY/FOR (160/7.2/4.8 mcg) pMDI, two inhalations twice daily = FF/UMEC/VI (100/62.5/25 mcg) DPI, one inhalation once daily.

The proposed equi-effective doses are consistent with the recommended doses in the draft/approved PIs, and the clinical evidence presented in the submission.

6.26 Table 6 presents the results of the cost-minimisation analysis, based on drug costs only over one year (and 100% compliance for both treatments). As both BUD/GLY/FOR and FF/UMEC/VI provide for the same duration of treatment, and the cost-minimisation analysis only included drug costs, the requested price for BUD/GLY/FOR is the same as the current price for FF/UMEC/VI (AEMP: $[redacted]).

Table 6: Results of the cost-minimisation analysis

Component	BUD/GLY/FOR (160/7.2/5)	FF/UMEC/VI (100/62.5/25)
AEMP / pack	$[redacted]	$[redacted]
Dose	Two inhalations twice daily	One inhalation once daily
Units / day	4 actuations	1 actuation
Units / pack	1 x 120 actuations	1 x 30 actuations
Days / pack	30 days	30 days
Scripts / year (365 days)	12.17	12.17
Total cost / year	$[redacted]	$[redacted]

Abbreviations: AEMP=approved ex-manufacturer price; BUD=budesonide; FF=fluticasone fumarate; FOR=formoterol fumarate dihydrate; GLY=glycopyrronium; UMEC=umeclidinium; VI=vilanterol trifenatate;
Source: Table 2.8.2, pp93-94 of the submission.

6.27 Under Section 101(3B) of the National Health Act (1953), the PBAC cannot recommend listing a therapy that is substantially more costly than an alternative therapy unless it is satisfied that the therapy provides, for some patients, a significant improvement in efficacy and/or reduction in toxicity. For the purposes of satisfying Section 101(3B), the PBAC has considered that the cost for any triple therapy FDC inhalers should be no greater than the lowest price combination of ICS, LAMA and LABA products listed for COPD (paragraph 7.8, Trelegy (FF/UMEC/VI) PSD December 2017 PBAC meeting; paragraph 7.2, Trimbow (BEC/GLY/FOR) PSD November 2020 PBAC meeting).

6.28 A further cost-minimisation analysis was conducted during the evaluation versus open combinations of ICS, LAMA and LABA inhalers available on the PBS for COPD. This analysis included single component ICS inhalers, which have unrestricted listing on the PBS listings but are not TGA registered for COPD. These inhalers are relevant comparators because i) the clinical guidelines recommend 'adding ICS' when stepping up to triple therapy and ii) 'off label' use can be regarded as 'standard medical management' for this purpose under Section 1.1.3 of the PBAC Guidelines. However, in the absence of acceptable equi-effective doses for COPD, only single ICS inhalers containing equivalent doses of BUD and FF as provided in BUD/GLY/FOR and FF/UMEC/VI respectively, were considered. The pre-PBAC response (p1) argued that single component inhalers, which have an unrestricted listing on the PBS but are not TGA registered for COPD, are not relevant comparators. The pre-PBAC response (p1) argued that there is no dosing schedule to guide appropriate dosing for COPD. In addition, the pre-PBAC stated the COPD-X Plan (2020) does not recommend LAMA/LABA + ICS single inhaler as a regimen for COPD maintenance and specifically includes a note ICS monotherapy is not indicated for COPD. As such, the pre-PBAC response (p1) argued that open triple multiple inhaler regimens which contain an ICS single inhaler are not 'standard medical management'. The PBAC recalled that in November 2020, it had recommended that the cost of BEC/GLY/FOR should be no greater than the lowest price combination of the PBS listed components of the triple therapy that are available for COPD (paragraphs 7.2, Trimbow (BEC/GLY/FOR) PSD November 2020 PBAC meeting).

6.29 Table 7 presents less costly combinations of ICS, LAMA and LABA products compared to BUD/GLY/FOR at the requested AEMP. The results illustrate that the individual components (BUD/FOR + GLY) as well as a number of other ICS, LAMA and LABA combinations were less costly alternatives, for 30 days of treatment.

Table 7: Combinations of ICS, LAMA and LABA inhalers available on the PBS for COPD that are less costly for 30 days of treatment than the requested price of BUD/GLY/FOR (AEMP = $[redacted])

	Units / day (at equi-effective doses)	Units / pack	Days / pack	AEMP	AEMP / 30 days
Individual components of BUD/GLY/FOR (160/7.2/5)					
BUD/FOR 200/6 (10018G) GLY 50 (10059K)	4 actuations 1 actuation	240 30	60 30	$55.75 $44.95	$72.83
Individual components, other combinations of ICS, LAMA and LABA inhalers					
FF/VI 100/25 (11124L) TIO 18 (8626B)	1 actuation 1 actuation	30 30	30 30	$41.88 $28.82	$70.70
FF 100 (11719T) TIO/OLO 2.5/2.5 (10557P)	1 actuation 2 actuations	30 60	30 30	$15.65 $57.27	$72.92
BUD 200 (2071B) TIO/OLO 2.5/2.5 (10557P)	4 actuations 2 actuations	200 60	50 30	$16.19 $57.27	$66.98

Abbreviations: ACL=aclidinium; BUD=budesonide; FF=fluticasone fumarate dihydrate; FOR=formoterol fumarate dihydrate; GLY=glycopyrronium; ICS=inhaled corticosteroids; IND=indacaterol; LABA=long acting beta-2 agonist; LAMA=long acting muscarinic antagonist; OLO=olodaterol; SAL=salmeterol; TIO=tiotropium; UMEC=umeclidinium; VI=vilanterol;
Source: Constructed during the evaluation using PBS pricing calculator (as of 1 July 2020) 7CPA v33.xlsm.

6.30 The ESC noted the AEMP for the recently PBS listed BEC/GLY/FOR (Trimbow) was $70.70.

Drug cost/patient/year: $[redacted]

6.31 Assuming a DPMQ of $[redacted] (AEMP $[redacted]) and 12.17 scripts required for one year of treatment with BUD/GLY/FOR 160/7.2/5 two inhalations twice daily, the cost per patient per year is $[redacted].

Estimated PBS usage & financial implications

6.32 The submission was not considered by DUSC. The submission applied a market share approach to estimate the financial impact of the proposed listing of BUD/GLY/FOR on the PBS for moderate to severe COPD. The analysis assumed the patients eligible for BUD/GLY/FOR are the same patients currently eligible for FF/UMEC/VI.

6.33 The financial estimates used historical PBS utilisation data for FF/UMEC/VI in COPD to estimate the projected growth of the triple therapy FDC market, given FF/UMEC/VI is currently the only FDC triple therapy listed on the PBS. The submission assumed that the projected growth in scripts of FF/UMEC/VI captures all patients with uncontrolled COPD despite maintenance dual therapy or those who switch from open triple therapy to FDC triple therapy. The submission also assumed that the proposed listing of BUD/GLY/FOR would not grow the triple therapy ICS/LAMA/LABA market, identical compliance rates (i.e. same compliance for once daily and twice daily dosing regimens) and that BUD/GLY/FOR will displace FF/UMEC/VI in a 1:1 ratio. The ESC noted that, like BEC/GLY/FOR, BUD/GLY/FOR is delivered via a pMDI whereas FF/UMEC/VI is available in a DPI. The ESC considered that availability of COPD triple therapy in a pMDI may potentially grow the triple therapy ICS/LAMA/LABA market. In addition, as BUD/GLY/FOR contains FOR, the ESC considered there was also the potential for use outside of the proposed indication for patients with asthma (see paragraph 3.4).

6.34 Table 8 summarises the key inputs in the financial estimates.

Table 8: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Total ICS/LAMA/LABA FDC market (scripts)	Yr 0 (2020): 458,448 Source: PBS/RPBS services for FF/UMEC/VI (Trelegy Ellipta) June 2018 to December 2020	Reasonable, although the submission assumed Yr 1 of listing as 2021.
ICS/LAMA/LABA market growth	Yr 1: 40% to Yr 6: 7% Source: Assumption. The submission estimated the growth of COPD inhalers between 2017 to 2020 using data from Medicare statistics and the 10% Medicare sample. The analysis indicated 311% growth in use of FF/UMEC/VI in 2019 and 57% growth in 2020.	Reasonable. The predicted market growth of 40% to 7% over the first 6 years of listing was consistent with the assumed growth rate in the BEC/GLY/FOR submission (Yr 1: 40% to Yr 6: 4%), considered by the PBAC in November 2020 (Table 9, Trimbow (BEC/GLY/FOR) PSD November 2020 PBAC meeting).
BUD/GLY/FOR market share (i.e. FF/UMEC/VI displacement rate)	Yr 1: 15% to Yr 6: 36% Source: Assumption based on similar analogues	Generally reasonable, although the submission did not provide any data to support this assumption. The assumed market shares were similar to those assumed in the BEC/GLY/FOR submission (Yr 1: 7% to Yr 6: 31%), considered by the PBAC in November 2020 (Table 9, Trimbow (BEC/GLY/FOR) PSD November 2020 PBAC meeting).
BUD/GLY/FOR cost	$[redacted] Source: Requested DPMQ	Consistent with the cost-minimisation analysis presented in the submission.
FF/UMEC/VI cost	$[redacted] Source: Current DPMQ (Item 11379X)	Reasonable.

Abbreviations: COPD=chronic obstructive pulmonary disease; BUD=budesonide; DPMQ=dispensed price for maximum quantity; FDC=fixed dose combination; FF=fluticasone fumarate; FOR=formoterol fumarate dihydrate; GLY=glycopyrronium; ICS=inhaled corticosteroids; LABA=long acting beta-2 agonist; LAMA=long acting muscarinic antagonist; UMEC=umeclidinium; VI=vilanterol trifenatate.
Source: Table 4.1.1, p96 of the submission.

6.35 Table 9 summarises the estimated net financial implications for the proposed listing of BUD/GLY/FOR on the PBS/RPBS for COPD.

Table 9: Estimated use and financial implications to the PBS/RPBS of BUD/GLY/FOR COPD

	Year 1 2021	Year 2 2022	Year 3 2023	Year 4 2024	Year 5 2025	Year 6 2026
Total ICS/LAMA/LABA market, FF/UMEC/VI scripts	[redacted][1]	[redacted][2]	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]
Estimated use and financial implications of the proposed medicine on the PBS/RPBS						
BUD/GLY/FOR						
Total scripts	[redacted][5]	[redacted][6]	[redacted][6]	[redacted][7]	[redacted][8]	[redacted][8]
PBS/RPBS cost	$[redacted][9]	$[redacted][10]	$[redacted][11]	$[redacted][12]	$[redacted][13]	$[redacted][13]
PBS/RPBS net cost (less co-pay)	$[redacted][9]	$[redacted][10]	$[redacted][11]	$[redacted][12]	$[redacted][12]	$[redacted][13]
Estimated change in use and financial implications for other comparators						
FF/UMEC/VI						
Total scripts	-[redacted][5]	-[redacted][6]	-[redacted][6]	-[redacted][7]	-[redacted][8]	-[redacted][8]
PBS/RPBS cost	-$[redacted][9]	-$[redacted][10]	-$[redacted][11]	-$[redacted][12]	-$[redacted][13]	-$[redacted][13]
PBS/RPBS net cost (less co-pay)	-$[redacted][9]	-$[redacted][10]	-$[redacted][11]	-$[redacted][12]	-$[redacted][12]	-$[redacted][13]
Net financial implications for the PBS/RPBS and the Health budget						
PBS/RPBS cost	$[redacted][9]	$[redacted][9]	$[redacted][9]	$[redacted][9]	$[redacted][9]	$[redacted][9]
PBS/RPBS net cost (less co-pay)	$[redacted][9]	$[redacted][9]	$[redacted][9]	$[redacted][9]	$[redacted][9]	$[redacted][9]

Abbreviations: COPD=chronic obstructive pulmonary disease; BUD=budesonide; FF=fluticasone fumarate; FOR=formoterol fumarate dihydrate; GLY=glycopyrronium; UMEC=umeclidinium; VI=vilanterol trifenatate.

Source: Tables 4.2.2 to 4.5.1, pp98-102 of the submission.

The redacted values correspond to the following ranges:

[1] *600,000 to < 700,000*
[2] *800,000 to < 900,000*
[3] *900,000 to < 1,000,000*
[4] *1,000,000 to < 2,000,000*
[5] *90,000 to < 100,000*
[6] *200,000 to < 300,000*
[7] *300,000 to < 400,000*
[8] *400,000 to < 500,000*
[9] *$0 to < $10 million*
[10] *$10 million to < $20 million*
[11] *$20 million to < $30 million*
[12] *$30 million to < $40 million*
[13] *$40 million to < $50 million*

6.36 At the requested price (DPMQ $[redacted]), the proposed listing of BUD/GLY/FOR was estimated to be cost neutral to the PBS/RPBS. The estimated cost savings from FF/UMEC/VI completely offsets the estimated cost of BUD/GLY/FOR ($100 million to < $200 million over the first six years of listing).

6.37 If BUD/GLY/FOR was listed based on a cost-minimisation analysis to the least costly combination of the components (i.e. ICS, LAMA and LABA inhalers), which was lower than the requested price, then the proposed listing would be cost-saving to the PBS/RPBS assuming no change to the current background growth or compliance rates.

Quality Use of Medicines

6.38 The submission stated that the sponsor would provide patient and prescriber education on the appropriate use of BUD/GLY/FOR and continue to support Lung Foundation Australia on activities aimed at achieving these goals.

Financial Management – Risk Sharing Arrangements

6.39 The sponsor did not propose a RSA for BUD/GLY/FOR. At the November 2020 meeting, the PBAC considered that while the AEMP for BEC/GLY/FOR would be lower than

FF/UMEC/VI, the two products were considered non-inferior and anticipated to substitute in the COPD market. At that time, the PBAC also recalled that at its December 2017 meeting that FF/UMEC/VI would be acceptably cost-effective if its price was not substantially greater than the price of LAMA/LABA dual therapy and recommended that a small price advantage be negotiated over the price of currently listed LAMA/LABA FDCs (paragraph 7.1, Trelegy Ellipta PSD, December 2017 PBAC meeting). As such, in November 2020 the PBAC considered it appropriate that BEC/GLY/FOR be subject to the RSA currently in place for FF/UMEC/VI (paragraphs 7.7 to 7.8, Trimbow (BEC/GLY/FOR) PSD November 2020 PBAC meeting). The pre-PBAC response (p1) noted that the sponsor was amenable to the same listing options for BUD/GLY/FOR that were available for BEC/GLY/FOR.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC recommended the Authority Required (STREAMLINED) listing of the fixed dose combination (FDC) of budesonide (BUD) with glycopyrronium (GLY) and formoterol (FOR), for maintenance treatment of moderate to severe chronic obstructive pulmonary disease (COPD) that is not adequately treated by a combination of an inhaled corticosteroid (ICS) with long-acting beta2-agonist (LABA) or LABA with a long-acting muscarinic antagonist (LAMA).

7.2 The PBAC considered that the claim of non-inferior effectiveness and safety to the FDC of fluticasone furoate (FF), umeclidinium (UMEC) and vilanterol (VIL), was reasonable. However, the PBAC considered for the purposes of satisfying Section 101(3B) of the *National Health Act 1953*, FF/UMEC/VIL, BEC/GLY/FOR, as well as any triple combination therapy via concomitant use of a LAMA, LABA and ICS are relevant alternative therapies. The PBAC's recommendation was therefore, among other matters, based on its assessment that the cost of BUD/GLY/FOR should be no greater than the lowest price combination of the PBS listed components of the triple therapy that are available for COPD, and that BUD/GLY/FOR should be subject to the same risk sharing arrangements as are currently in place for the triple therapy FDCs for COPD.

7.3 The PBAC noted the input from Lung Foundation Australia supporting the listing of BUD/GLY/FOR maintenance treatment of COPD.

7.4 The PBAC considered the nomination of FF/UMEC/VIL as the main comparator and BEC/GLY/FOR as a near market comparator appropriate. In addition, the PBAC also considered that triple therapy via concomitant use of any combination of LAMA, LABA and ICS were appropriate alternative therapies.

7.5 The PBAC noted that the claim of non-inferior effectiveness for BUD/GLY/FOR compared to FF/UMEC/VI and BEC/GLY/FOR was based on an indirect comparison of annual COPD exacerbation rates, change in morning pre-dose trough FEV1, change in St George's Respiratory Questionnaire and change in use of daily rescue medication. The indirect treatment comparisons used either ICS/LABA or LAMA/LABA FDC inhalers as the common reference, based on the assumption that different agents from the same class have comparable efficacy and safety. The PBAC considered this assumption was reasonable and consistent with past decisions. The PBAC agreed with ESC that overall the claim of non-inferior effectiveness was supported by the indirect evidence

presented in the submission.

7.6 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

7.7 The PBAC noted that the submission presented a cost-minimisation analysis between BUD/GLY/FOR and FF/UMEC/VI and accepted the following equi-effective doses as the basis for the analysis:

BUD/GLY/FOR (160/7.2/4.8 mcg) two inhalations twice daily = FF/UMEC/VI (100/62.5/25 mcg) one inhalation once daily = BEC/GLY/FOR 100mcg/6mcg/10mcg two inhalations twice daily.

7.8 However, as outlined in paragraph 7.4, the PBAC considered that triple therapy via concomitant use of any combination of LAMA, LABA and ICS were appropriate alternative therapies. Under Section 101(3B) of the *National Health Act 1953*, the PBAC cannot recommend listing a therapy at a price that is substantially more costly than an alternative therapy unless it is satisfied that the therapy provides, for some patients, a significant improvement in efficacy or reduction in toxicity. Based on the same principle, the PBAC considered that the ceiling price for any fixed combination of triple therapy of ICS/LABA/LAMA should be no greater than the lowest price combination of any listed components of COPD triple therapy that are available for COPD. The PBAC noted that the AEMP for BUD/GLY/FOR would be lower than the current AEMP for FF/UMEC/VI (see paragraph 6.29) due to price reductions that have occurred for some components over time.

7.9 The PBAC considered that, while the AEMP for BUD/GLY/FOR would be lower than that of FF/UMEC/VI, the BUD/GLY/FOR, FF/UMEC/VI and BEC/GLY/FOR were considered non-inferior and anticipated to substitute in the COPD market. The PBAC considered it appropriate that BUD/GLY/FOR be subject to the same risk sharing arrangements currently in place for the triple therapy FDC comparators.

7.10 The PBAC recalled that at its December 2017 meeting, that FF/UMEC/VI would be acceptably cost-effective if its price was not substantially greater than the price of LAMA/LABA dual therapy and recommended that a small price advantage be negotiated over the price of currently listed LAMA/LABA FDCs (paragraph 7.1, Trelegy Ellipta PSD, December 2017 PBAC meeting). The PBAC considered that it was open to the sponsor of BUD/GLY/FOR to negotiate a lower price with the Department in line with the intent of the December 2017 Trelegy Ellipta recommendation, while ensuring it does not exceed the ceiling price criteria set out in paragraph 7.8, to mitigate the requirement for a risk sharing arrangement.

7.11 The PBAC noted the financial estimates would need to be recalculated to take into account the outcome of its considerations regarding the cost-minimisation analysis.

7.12 The PBAC noted that BUD/GLY/FOR contains FOR, a LABA with a short duration of action used for the relief of symptoms in the asthma setting. The PBAC agreed with the ESC that it would be appropriate to convey in the listing that this product is not indicated as reliever therapy and that the listing is intended to facilitate regular, twice daily dosing as per the approved Product Information. The PBAC considered the circumstances of PBS eligibility applicable to all three triple therapy FDCs for COPD

should be no different and as such flow-on restriction changes would also be required for BEC/GLY/FOR and FF/UMEC/VI as outlined in paragraph 8.2.

7.13 The PBAC advised that under Section 101(3BA) of the *National Health Act 1953* BUD/GLY/FOR should be treated as interchangeable on an individual patient basis with FF/UMEC/VI and BEC/GLY/FOR.

7.14 The PBAC advised that BUD/GLY/FOR is suitable for prescribing by nurse practitioners as continuing therapy only.

7.15 The PBAC recommended that the Early Supply Rule should apply to BUD/GLY/FOR.

7.16 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because BUD/GLY/FOR is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over FF/UMEC/VI, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.

7.17 The PBAC noted that this submission is not eligible for an Independent Review, as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new medicinal product as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
BUDESONIDE + FORMOTEROL (EFORMOTEROL) + GLYCOPYRRONIUM					
budesonide 160 microgram/actuation + glycopyrronium 7.2 microgram/actuation + formoterol (eformoterol) fumarate dehydrate 5 microgram/actuation inhalation, 120 actuations	NEW	1	1	5	Breztri Aerosphere 160/7.2/5
Restriction Summary / Treatment of Concept: [New 1]					
	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: ☒ Medical Practitioners ☒ Nurse practitioners - CTO				
	Restriction type: ☒ Authority Required (STREAMLINED) [New 1]				
	Administrative Advice: **Continuing Therapy Only:** For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.				
	Indication: Chronic obstructive pulmonary disease (COPD)				
	Treatment Phase: [blank]				
	Clinical criteria:				
	Patient must have experienced at least one severe COPD exacerbation, which required hospitalisation, or two or more moderate exacerbations in the previous 12 months, with significant symptoms despite regular bronchodilator therapy with a long acting muscarinic antagonist (LAMA) and a long acting beta-2 agonist (LABA) or an inhaled corticosteroid (ICS) and a LABA; or				
	Patient must have been stabilised on a combination of a LAMA, LABA and an ICS for this condition				
	AND				
	Treatment criteria:				
	Patient must not be undergoing treatment with this product in each of the following circumstances: (i) treatment of asthma in the absence of a COPD diagnosis, (ii) initiation of bronchodilator therapy in COPD, (iii) use as reliever therapy for asthma, (iv) dosed at an interval/frequency that differs to that recommended in the approved Product Information				
	Administrative Advice: Formal assessment and correction of inhaler technique should be performed in accordance with the COPD-X Plan (available at http://copdx.org.au/); the assessment and adherence to correct technique should be documented in the patient's medical records.				
	Administrative Advice: Diagnosis of COPD should include measurement of airflow obstruction using spirometry, with confirmation of post-bronchodilator airflow obstruction.				
	Administrative Advice: The treatment must not be used in combination with an ICS/LABA, LABA/LAMA or LAMA, LABA or ICS monotherapy.				
	Administrative Advice: A LAMA includes tiotropium, glycopyrronium, aclidinium or umeclidinium.				
	Administrative Advice: A LABA includes olodaterol, indacaterol, salmeterol, formoterol or vilanterol.				
	Administrative Advice: An ICS includes fluticasone propionate, fluticasone furoate, budesonide, beclometasone or ciclesonide.				

8.2 Flow on changes to BEC/GLY/FOR and FF/UMEC/VIL listings in COPD as outlined in paragraph 7.12 to convey that the product is not intended to be used solely as a symptom reliever, and not to be dosed at a frequency/schedule outside that specified in the Product Information, are as follows.

Edit Restriction Summary 11676 / Treatment of Concept: 10167 to form New 1 *(current as at 1 July 2021; only relevant edits shown below)*	
MEDICINAL PRODUCT: **medicinal product pack:** **(Available brand):**	**PBS item code/s**
FLUTICASONE FUROATE + UMECLIDINIUM + VILANTEROL fluticasone furoate 100 microgram/actuation + umeclidinium 62.5 microgram/actuation + vilanterol 25 microgram/actuation powder for inhalation, 30 actuations (Trelegy Ellipta 100/62.5/25)	11379X
BECLOMETASONE + FORMOTEROL (EFORMOTEROL) + GLYCOPYRRONIUM beclometasone dipropionate 100 microgram/actuation + formoterol (eformoterol) fumarate dihydrate 6 microgram/actuation + glycopyrronium 10 microgram/actuation inhalation, 120 actuations (Trimbow)	12468F
~~**Administrative Advice:**~~ ~~This product is not PBS-subsidised for the treatment of asthma or the initiation of bronchodilator therapy in COPD.~~	
Treatment criteria:	
Patient must not be undergoing treatment with this product in each of the following circumstances: (i) treatment of asthma in the absence of a COPD diagnosis, (ii) initiation of bronchodilator therapy in COPD, (iii) use as reliever therapy for asthma, (iv) dosed at an interval/frequency that differs to that recommended in the approved Product Information	

This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.