5.01 BECLOMETASONE WITH FORMOTEROL AND GLYCOPYRRONIUM,
Pressurised inhalation containing beclometasone dipropionate 100 micrograms with formoterol fumarate dihydrate 6 micrograms and glycopyrronium 10 micrograms (as bromide) per dose, 120 doses; Pressurised inhalation containing beclometasone dipropionate 200 micrograms with formoterol fumarate dihydrate 6 micrograms and glycopyrronium 10 micrograms (as bromide) per dose, 120 doses, Trimbow®,
Chiesi Australia Pty Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested an Authority Required (Streamlined) listing for a fixed dose combination (FDC) of beclometasone (BEC), an inhaled corticosteroid (ICS) with formoterol (FOR), a long-acting beta agonist (LABA) and glycopyrronium (GLY), a long-acting muscarinic antagonist (LAMA) for the maintenance therapy of severe asthma.

1.2 The proposed listing is for two strengths: medium dose BEC/FOR/GLY (100/6/10 µg) and high dose BEC/FOR/GLY (200/6/10 µg).

1.3 Listing was requested on the basis of a cost-minimisation analysis versus mometasone (MF) with indacaterol (IND) and glycopyrronium (GLY). Medium dose BEC/FOR/GLY was compared to medium dose MF/IND/GLY (68/114/46 µg) and high dose BEC/FOR/GLY was compared to high dose MF/IND/GLY (136/114/46 µg).

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Maintenance treatment of asthma in adult patients not adequately controlled with a maintenance combination of a LABA and an ICS who experienced one or more asthma exacerbations in the previous year.
Intervention	Beclometasone dipropionate (BEC) + formoterol fumarate dihydrate (FOR) + glycopyrronium (GLY). Medium dose: BEC/FOR/GLY (100/6/10 µg) - Each delivered dose (the dose leaving the mouthpiece) contains 87 µg BEC, 5 µg FOR and 9 µg GLY (as 11 µg glycopyrronium bromide). High dose: BEC/FOR/GLY (200/6/10 µg) - Each delivered dose (the dose leaving the mouthpiece) contains 172 µg BEC, 5 µg FOR and 9 µg GLY (as 11 µg glycopyrronium bromide).
Comparator	Medium dose: BEC/FOR/GLY (100/6/10 µg) - Primary comparator: mometasone furoate (MF) + indacaterol (IND) + glycopyrronium (GLY) (68/114/46 µg) - Clinical comparator: BEC/FOR (100/6 µg) High dose: BEC/FOR/GLY (200/6/10 µg) - Primary comparator: MF/IND/GLY (136/114/46 µg) - Near market comparator: fluticasone furoate (FF) + vilanterol (VI) + umeclidinium (UMEC) (200/25/62.5 µg) - Clinical comparators: BEC/FOR (200/6 µg) + tiotropium 2.5 µg; BEC/FOR (200/6 µg)
Outcomes	Efficacy: change from baseline in pre- and post-dose forced expiratory volume in 1 second (FEV1); pre-dose FEV1 response (change of ≥100 mL); change in average morning peak expiratory flow (PEF); rate of asthma exacerbations (moderate and severe) over treatment period; time to first asthma exacerbation; quality of life; asthma symptom-free days, asthma control days, days without rescue medication. Safety: Frequency of any adverse events (AEs); AEs related to study drug, AEs leading to study discontinuation, serious AEs, deaths, adverse events of special interest
Clinical claim	In adults with asthma who are not adequately controlled with a maintenance combination of a LABA and an ICS and who experienced one or more asthma exacerbations in the previous year, **Medium dose BEC/FOR/GLY (100/6/10 µg)** is: - Non-inferior in terms of efficacy and is non-inferior in terms of safety when compared to MF/IND/GLY (68/114/46 µg). - Superior in terms of efficacy (based on FEV) and is non-inferior in terms of safety when compared to BEC/FOR (100/6 µg). **High dose BEC/FOR/GLY (200/6/10 µg)** is: - Non-inferior in terms of efficacy and is non-inferior in terms of safety when compared to MF/IND/GLY (136/114/46 µg). - Non-inferior in terms of efficacy and is non-inferior in terms of safety when compared to FF/VI/UMEC (200/25/62.5 µg). - Non-inferior in terms of efficacy and is non-inferior in terms of safety when compared to BEC/FOR (200/6 µg) + tiotropium 2.5 µg. - Superior in terms of efficacy (based on FEV) and is non-inferior in terms of safety when compared to BEC/FOR (200/6 µg).

Source: Tables 2 & 54, pp7-9 & 137 and pp130-131 of the submission.

AEs = adverse events; BEC = beclometasone dipropionate; FEV1 = forced expiratory volume in one second; FF = fluticasone furoate; FOR = formoterol fumarate dihydrate; GLY = glycopyrronium; ICS = inhaled corticosteroid; IND = indacaterol; LABA = long-acting beta agonist; MF = mometasone furoate; PEF = peak expiratory flow; UMEC = umeclidinium; VI = vilanterol.

2 Background

Registration status

2.1 **TGA status at time of PBAC consideration**: Not registered.

2.2 BEC/FOR/GLY is not currently registered for asthma. The TGA application for BEC/FOR/GLY as treatment for asthma was lodged on 15 May 2021. At the time of evaluation for PBAC consideration, the TGA CER (Round 1) was available. The PBAC noted the TGA Delegate's Overview was not available at the time of consideration.

2.3 The proposed TGA indication for BEC/FOR/GLY is:

'Maintenance treatment of asthma in adult patients not adequately controlled with a maintenance combination of a long-acting beta-2 agonist and an inhaled corticosteroid who experienced one or more asthma exacerbations in the previous year.'

2.4 BEC/FOR/GLY was TGA registered on 24 June 2020 for chronic obstructive pulmonary disease (COPD).

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

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Add new indication of severe asthma (18274) to the current BEC/FOR/GLY 100 µg/6 µg/10 µg PBS listing (12468F) as follows:

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Dispensed price for Max. Qty**	**Available brands**
BECLOMETASONE + FORMOTEROL (EFORMOTEROL)+ GLYCOPYRRONIUM						
Beclometasone dipropionate 100 microgram/actuation + formoterol (eformoterol) fumarate 6 microgram/actuation + glycopyrronium 10 microgram/actuation inhalation, 120 actuations	12468F	1	1	5	$[redacted]	Trimbow
Restriction Summary: [11470] / Treatment of Concept: [11470] – *Copied from Enerzair Breezhaler's Restriction for severe asthma*						
	Category / Program: GENERAL – General Schedule (Code GE)					
	Prescriber type: ☒Medical Practitioners ☒Nurse practitioners					
	Restriction type: ☒Authority Required (Streamlined) [new/existing code]					
	Indication: Severe asthma					
	Clinical criteria:					
	~~Patient must have experienced at least one severe exacerbation, which has required documented use of systemic corticosteroids, in the previous 12 months while receiving optimised asthma therapy, despite formal assessment of and adherence to correct inhaler technique, which has been documented~~					

	Patient must have experienced at least one severe asthma exacerbation in the 12 months prior to having first commenced treatment for severe asthma, which required systemic corticosteroid treatment despite each of: (i) receiving optimised asthma therapy, (ii) being assessed for adherence to therapy, (iii) being assessed for correct inhaler technique.
	Population criteria:
	Patient must be aged 18 years or over
	Prescribing Instructions: *Optimised asthma therapy includes adherence to the maintenance combination of an inhaled corticosteroid (at least 800 micrograms budesonide per day or equivalent) and a long acting beta-2 agonist.*
	Administrative Advice: Formal assessment and correction of inhaler technique should be performed in accordance with the National Asthma Council (NAC) Information Paper for Health Professionals on Inhaler Technique (available at www.nationalasthma.org.au); the assessment and adherence to correct technique should be documented in the patient's medical records. Patients can obtain support with inhaler technique through their local Asthma Foundation (1800 645 130).
	Administrative Advice: This product is not indicated for the initiation of treatment in asthma
	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.

No changes will be made to the current PBS listing for the indication of COPD (9286), reproduced below:

Restriction Summary: [12349] / Treatment of Concept: [12349]	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners ☒Nurse practitioners
	Restriction type: ☒Authority Required (Streamlined) [new/existing code]
	Indication: Chronic obstructive pulmonary disease (COPD)
	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
	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: An ICS includes fluticasone propionate, fluticasone furoate, budesonide, beclometasone or ciclesonide.

	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.

Add new medicinal product pack (new strength: 200 µg/6 µg/10 µg) for the indication of severe asthma (18274) as follows:

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Dispensed price for Max. Qty**	**Available brands**
BECLOMETASONE + FORMOTEROL (EFORMOTEROL)+ GLYCOPYRRONIUM						
Beclometasone dipropionate 200 microgram/actuation + formoterol (eformoterol) fumarate 6 microgram/actuation + glycopyrronium 10 microgram/actuation inhalation, 120 actuations	NEW	1	1	5	$[redacted]	Trimbow

Restriction Summary: New/ Treatment of Concept: New – *based on Enerzair Breezhaler's Restriction for severe asthma*	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners ☒Nurse practitioners
	Restriction type: ☒Authority Required (Streamlined) [new/existing code]
	Indication: Severe asthma
	Clinical criteria:
	~~Patient must have experienced at least one severe exacerbation, which has required documented use of systemic corticosteroids, in the previous 12 months while receiving optimised asthma therapy, despite formal assessment of and adherence to correct inhaler technique, which has been documented~~
	Patient must have experienced at least one severe asthma exacerbation in the 12 months prior to having first commenced treatment for severe asthma, which required systemic corticosteroid treatment despite each of: (i) receiving optimised asthma therapy, (ii) being assessed for adherence to therapy, (iii) being assessed for correct inhaler technique.
	Population criteria:
	Patient must be aged 18 years or over
	Prescribing Instructions: *Optimised asthma therapy includes adherence to the maintenance combination of an inhaled corticosteroid (at least 800 micrograms budesonide per day or equivalent) and a long acting beta-2 agonist.*
	Administrative Advice: Formal assessment and correction of inhaler technique should be performed in accordance with the National Asthma Council (NAC) Information Paper for Health Professionals on Inhaler Technique (available at www.nationalasthma.org.au); the assessment and adherence to correct technique should be documented in the patient's medical records. Patients can obtain support with inhaler technique through their local Asthma Foundation (1800 645 130).
	Administrative Advice: This product is not indicated for the initiation of treatment in asthma
	Administrative Advice: *This pharmaceutical benefit is not for the treatment of chronic obstructive pulmonary disease*
	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 submission did not propose any special pricing arrangements.

3.3 The price requested for medium dose BEC/FOR/GLY (DPMQ $[redacted]) as treatment for severe asthma is lower than the current DPMQ for medium dose BEC/FOR/GLY as treatment for COPD (PBS item 12468F, DPMQ $88.10). The submission requested two separate PBS item numbers for medium dose BEC/FOR/GLY to preserve the current DPMQ for the COPD indication. This request is inconsistent with the BEC/FOR submission for COPD, also considered at the March 2022 PBAC meeting, which requested a single price for both the COPD and asthma indications, estimated according to the predicted use in the two indications. The Pre-Sub-Committee Response (PSCR) noted that for the COPD indication, the medium dose BEC/FOR/GLY (100/6/10 µg) is part of a risk sharing arrangement (RSA) with other triple FDC products. The PSCR stated this was the rationale for requesting separate PBS item codes for the COPD and asthma indications, as it would allow utilisation to be tracked separately for each indication to assist with the administration of the COPD RSA.

3.4 The proposed restriction is an Authority – Streamlined listing. The PBAC recently recommended the Authority Required (Streamlined) listing of fluticasone furoate with umeclidinium and vilanterol (FF/VI/UMEC) fixed dose combination for maintenance therapy of severe asthma, with flow-on restriction changes to the MF/IND/GLY listings for severe asthma (fluticasone furoate with umeclidinium and vilanterol, PBAC meeting outcomes, November 2021 PBAC meeting)[1]. The proposed restriction is consistent with recent PBAC advice.

3.5 The proposed clinical and population criteria are consistent with the existing restrictions for medium and high dose MF/IND/GLY as treatment for severe asthma (PBS items 12295D and 12298G).

3.6 The PBAC agreed with the pre-PBAC response that the changes proposed by the Secretariat to the clinical criteria were appropriate and consistent with the flow-on changes from the November 2021 recommendation of FF/VI/UMEC (paragraph 3.4, FF/VI/UMEC Public Summary Document [PSD], November 2021 PBAC Meeting).

3.7 The PBAC also considered the prescribing instructions defining optimised asthma therapy added by the Secretariat appropriate.

3.8 The proposed administrative advice is consistent with PBS items 12295D and 12298G, except PBS items 12295D and 12298G include a note "this drug is not PBS-listed for the treatment of chronic obstructive pulmonary disease (COPD)". Since medium dose BEC/FOR/GLY is PBS-subsidised for COPD (PBS item 12468F), this omission is appropriate.

3.9 The proposed restriction is narrower than the proposed TGA indication, which does not define the clinical criteria of exacerbations as severe, requiring documented use of systemic corticosteroids.

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[1] https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2021-11/pbac-web-outcomes-11-2021.pdf [accessed 12-Jan-2022]

3.10 The proposed restriction is not consistent with the trial evidence presented for BEC/FOR/GLY in the clinical section. The BEC/FOR/GLY trials did not require patients to be treated with systemic corticosteroids in the previous 12 months. A clinical practice note from the Australian Asthma Handbook (Table: Severity classification for flare-ups (exacerbations))[2] appears to support the submission's claim that differences in the definition of 'severe asthma' between the TRIMARAN/TRIGGER and the proposed restriction may not be relevant to clinical practice.

3.11 The proposed restriction is consistent with the cost-minimisation analysis presented and the estimation of use and budget impact estimates.

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

4 Population and disease

4.1 Asthma is a chronic inflammatory disease of the airways that is defined clinically as the presence of airflow limitation and respiratory symptoms (e.g., wheeze, shortness of breath, cough, chest tightness) that vary over time. The primary goal of asthma pharmacotherapy is to reduce the underlying inflammation and promote bronchodilation.

4.2 Asthma severity is determined by the type and amount of treatment needed to maintain adequate symptom control, with more serious disease requiring a greater intensity of treatment. Pharmacological management involves a stepwise approach for mild to moderate asthma and a targeted approach for severe asthma.

4.3 In the current Australian guidelines (Australian Asthma Handbook, 2020), severe asthma is defined as asthma that remains uncontrolled despite high dose ICS plus LABA (with correct inhaler technique and good adherence) or maintenance oral corticosteroids, or that requires such treatment to prevent it from becoming uncontrolled. Patients who experience exacerbations or uncontrolled asthma despite medium and high dose ICS/LABA can trial triple ICS/LABA/LAMA treatment. In the Australian and international guidelines, medium dose ICS includes 800 µg of budesonide per day or equivalent (at the upper dosage limit), and high dose ICS refers to more than 800 µg of budesonide per day or equivalent.

4.4 The submission proposed that BEC/FOR/GLY would be an alternative ICS/LABA/LAMA treatment for patients with severe asthma. ICS/LABA/LAMA treatments are currently available as a fixed dose combination (e.g., MF/IND/GLY) and medium or high dose ICS/LABA treatment with add-on LAMA (e.g., tiotropium). Tiotropium is the only PBS-listed LAMA therapy for asthma.

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

[2] https://www.asthmahandbook.org.au/management/adults/flare-ups [accessed 26-Nov-21]

5 Comparator

5.1 The submission nominated medium dose MF/IND/GLY (68/114/46 µg) as the main comparator for medium dose BEC/FOR/GLY (100/6/10 µg) and high dose MF/IND/GLY (136/114/46 µg) as the main comparator for high dose BEC/FOR/GLY (200/6/10 µg). The submission nominated high dose FF/VI/UMEC (200/25/62.5 µg) as a near market comparator for high dose BEC/FOR/GLY (200/6/10 µg). The proposed main and near-market comparators are appropriate. The submission included additional clinical comparisons versus other PBS listed alternative treatments (Table 1).

5.2 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect.

5.3 For the requested population, the following PBS-listed medicines may be considered alternative therapies because they could be replaced in practice: MF/IND/GLY and the following ICS/LABA combinations with tiotropium: budesonide with formoterol (BUD/FOR), fluticasone propionate with salmeterol (FP/SAL), fluticasone furoate with vilanterol (FF/VI), fluticasone propionate with formoterol (FP/FOR), mometasone furoate with indacaterol (MF/IND), beclometasone with formoterol (BEC/FOR).

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.

Consumer comments

6.2 The PBAC noted and welcomed the input from organisations (1) via the Consumer Comments facility on the PBS website. The comments from Asthma Australia described a range of benefits of treatment with BEC/FOR/GLY including that, if approved, it will increase treatment options particularly for eligible patients preferring metered-dose inhaler (MDI) devices.

Clinical trials

6.3 The submission was based on the following trials and studies involving BEC/FOR/GLY:

- One randomised trial comparing medium dose BEC/FOR/GLY with medium dose BEC/FOR: TRIMARAN (N=1,155).

- One randomised trial comparing high dose BEC/FOR/GLY with high dose BEC/FOR and high dose BEC/FOR + tiotropium 2.5µg: TRIGGER (N=1,437).

6.4 The submission also presented the following trials and studies involving other triple therapies:

- One randomised trial comparing medium dose MF/IND/GLY to medium dose MF/IND and high dose MF/IND/GLY to high dose MF/IND and high dose FP/SAL: IRIDIUM (N=3,092).
- One randomised trial comparing medium dose MF/IND/GLY to high dose MF/IND/GLY and high dose FP/SAL + tiotropium 5µg: ARGON (N=1,426).
- One randomised trial comparing medium and high dose FF/VI with medium and high dose FF/VI/UMEC 31.25µg and medium and high dose FLU/VI/UMEC 62.5µg: CAPTAIN (N=2,439).
- Two published meta-analyses of randomised controlled trials where at least one arm included a triple ICS/LABA/LAMA or ICS/LABA plus LAMA therapy: Rogliani et. al (2021) and Kim et. al. (2021).

6.5 The IRIDIUM, ARGON and CAPTAIN trials were included in the MF/IND/GLY submission considered by the PBAC at the July 2020 PBAC meeting. The TRIGGER, IRIDIUM, ARGON, and CAPTAIN trials were included in the FF/VI/UMEC submission considered by the PBAC at the November 2021 PBAC meeting.

6.6 The PrimoTinA trials (1 & 2) comparing pooled medium/high dose multiple inhaler triple therapy (ICS/LABA + tiotropium) and pooled medium/high dose ICS/LABA therapy were not included in this submission because the literature searches were restricted to only consider fixed dose combination ICS/LABA/LAMA (and not ICS/LABA plus separately administered LAMA therapy). PrimoTinA 1 & 2 were included in the meta-analysis by Kim et. al (2021), which was included in this submission.

6.7 Details of the trials presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
BEC/FOR/GLY trials		
Trimaran NCT02676076	A 52 week, randomized, double blind, multinational, multicentre, active controlled, 2-arm parallel group trial comparing CHF 5993 100/6/12.5µg pMDI (fixed combination of extrafine beclometasone dipropionate plus formoterol fumarate plus glycopyrronium bromide) to CHF 1535 100/6µg pMDI (fixed combination of extrafine beclomethasone dipropionate plus formoterol fumarate) in patients with asthma uncontrolled on medium doses of Inhaled corticosteroids in combination with long-acting ß2-agonists. Virchow JC, Paggiaro P, Canonica WG, Kuna P, Kots M, Corre S, Vele A, Georges G, Petruzzelli S. Effect of extrafine medium strength (MS) ICS-containing triple therapy on exacerbations in asthmatics with persistent airflow limitation: A post-hoc analysis of the TRIMARAN study.	24 January 2019 European Respiratory Journal 2019; 54 (Supplement 63).

Trial ID	Protocol title/ Publication title	Publication citation
	Paggiaro P, Kuna P, Kots M, Corre S, Carzana E, Vele A, Georges G, Petruzzelli S, Virchow JC. Efficacy and safety of a fixed combination extrafine beclomethasone dipropionate, formoterol fumarate, and glycopyrronium bromide (BDP/FF/GB) pMDI treatment compared to fixed combination BDP/FF in patients with uncontrolled asthma on medium dose ICS/LABA: the TRIMARAN study.	American Journal of Respiratory and Critical Care Medicine 2019; 199:9.
TRIGGER NCT02676089	A 52 week, randomized, double blind, multinational, multicentre, active controlled, 3-arm parallel group trial comparing CHF 5993 200/6/12.5µg pMDI (fixed combination of extrafine beclometasone dipropionate plus formoterol fumarate plus glycopyrronium bromide) to CHF 1535 200/6µg pMDI (fixed combination of extrafine beclomethasone dipropionate plus formoterol fumarate) alone or on top of open-label tiotropium 2.5µg Respimat® in patients with asthma uncontrolled on high doses of inhaled corticosteroids in combination with long-acting β2-agonists.	30 January 2019
	Singh D, Virchow JC, Canonica WG, Georges G, Vele A, Nudo E, Guller P, Papi A. Effect of high ICS dose fixed combination extrafine beclomethasone dipropionate, formoterol fumarate, and glycopyrronium (BDP/FF/G) pMDI on asthma control in patients with persistent airflow limitation (PAL): a post-hoc analysis of the TRIGGER study.	Thorax 2021; 76 (Supplement 1):A19-A20.
	Canonica WG, Virchow JC, Singh D, Kots M, Zuccaro F, Vele A, Georges G, Petruzzelli S. Effect of high extrafine strength (HS) ICS-containing triple therapy on exacerbations in patients with severe asthma and persistent airflow limitation: Post-hoc analysis of the TRIGGER study.	European Respiratory Journal 2019; 54 (Supplement 63).
	Canonica WG, Virchow JC, Kots M, Zuccaro F, Carzana E, Vele A, Georges G, Petruzzelli S. Efficacy and safety of high ICS dose fixed-combination ICS/LABA/LAMA pMDI compared with ICS/LABA and ICS/LABA+ LAMA in patients with uncontrolled asthma: the TRIGGER study.	American Journal of Respiratory and Critical Care Medicine 2019; 199:9.
TRIMARAN and TRIGGER	Virchow JC, Kuna P, Paggiaro P, Papi A, Singh D, Corre S, Zuccaro F, Vele A, Kots M, Georges G, Petruzzelli S. Single inhaler extrafine triple therapy in uncontrolled asthma (TRIMARAN and TRIGGER): two double-blind, parallel-group, randomised, controlled phase 3 trials.	The Lancet 2019; 394(10210):1737-49.
	Papi A, Virchow JC, Singh D, Kots M, Vele A, Georges G, Canonica GW. Extrafine triple therapy and asthma exacerbation seasonality: TRIMARAN and TRIGGER post hoc analyses.	J Allergy Clin Immunol. 2021; 148(1):262-265.e2.
	Virchow JC, Singh D, Canonica WG, Vele A, Georges G, Papi A. Normalization of Airflow Obstruction with Extra Fine Beclomethasone Dipropionate, Formoterol Fumarate, and Glycopyrronium Bromide (BDP/FF/GB) pMDI: A Post-Hoc Analysis of the TRIMARAN and TRIGGER Studies.	American Journal of Respiratory and Critical Care Medicine 2021; 203:9.
	Singh D, Virchow JC, Cononica W, Vele A, Georges G, Papi A. Persistent Airflow Limitation and the Risk for Moderate-Severe Asthma Exacerbations: A Post-Hoc Analysis of the TRIMARAN and TRIGGER Studies.	American Journal of Respiratory and Critical Care Medicine 2021; 203:9.
	Singh D, Virchow JC, Canonica GW, Vele A, Kots M, Georges G, Papi A. Determinants of response to inhaled extrafine triple therapy in asthma: analyses of TRIMARAN and TRIGGER.	Respiratory research 2020; 21(1):1-1.

Trial ID	Protocol title/ Publication title	Publication citation
	Papi A, Singh D, Virchow CJ, Kots M, Vele A, Georges G, Canonica GW. Effect of triple therapy with extra-fine BDP/FF/GB pMDI during seasonal peaks of asthma exacerbations. A post-hoc analysis of the TRIMARAN and TRIGGER studies. Singh D, Virchow JC, Canonica WG, Corre S, Zuccaro F, Kots M, Vele A, Georges G, Petruzzelli S. Characteristics of prominent response to triple therapy in patients with asthma uncontrolled on ICS/LABA: A stratified analysis of the TRIMARAN and TRIGGER studies. Virchow JC, Canonica WG, Paggiaro P, Kots M, Corre S, Zucarro F, Carzana E, Vele A, Georges G, Petruzzelli S. Reducing the rate of severe asthma exacerbations using single-inhaler extrafine BDP/FF/GB combination compared to BDP/FF in patients with uncontrolled asthma: pooled results from the TRIMARAN and TRIGGER studies.	European Respiratory Journal 2020; 56 (Supplement 64). European Respiratory Journal 2019; 54 (Supplement 63). American Journal of Respiratory and Critical Care Medicine 2019; 199:9.
MF/IND/GLY trials		
IRIDIUM NCT02571777	Kerstjens HAM, Maspero J, Chapman KR, van Zyl-Smit RN, Hosoe M, Tanase AM, Lavecchia C, Pethe A, Shu X, D'Andrea P. Once-daily, single-inhaler mometasone-indacaterol-glycopyrronium versus mometasone-indacaterol or twice-daily fluticasone-salmeterol in patients with inadequately controlled asthma (IRIDIUM): a randomised, double-blind, controlled phase 3 study.	Lancet Respir Med. 2020; 8(10):1000-1012.
ARGON NCT03158311	Gessner C, Kornmann O, Maspero J, van Zyl-Smit R, Krüll M, Salina A, Gupta P, Bostel S, Fucile S, Conde LG, Pfister P. Fixed-dose combination of indacaterol/glycopyrronium/mometasone furoate once-daily versus salmeterol/fluticasone twice-daily plus tiotropium once-daily in patients with uncontrolled asthma: A randomised, Phase IIIb, non-inferiority study (ARGON).	Respir Med. 2020; 170:106021.
FF/VI/UMEC trials		
CAPTAIN NCT02924688	Lee LA, Bailes Z, Barnes N, Boulet LP, Edwards D, Fowler A, Hanania NA, Kerstjens HAM, Kerwin E, Nathan R, Oppenheimer J, Papi A, Pascoe S, Brusselle G, Peachey G, Sule N, Tabberer M, Pavord ID. Efficacy and safety of once-daily single-inhaler triple therapy (FF/UMEC/VI) versus FF/VI in patients with inadequately controlled asthma (CAPTAIN): a double-blind, randomised, phase 3A trial.	Lancet Respir Med. 2021; 9(1):69-84.
Systematic reviews/meta-analyses		
TRIMARAN, TRIGGER, IRIDIUM, ARGON, CAPTAIN	Rogliani P, Ritondo B.L, Calzetta L. Triple therapy in uncontrolled asthma: a network meta-analysis of Phase III studies.	Eur Respir J. 2021; 58(3):2004233.
TRIMARAN, TRIGGER, IRIDIUM, CAPTAIN	Kim L.H.Y, Saleh C, Whalen-Browne A, O'Byrne P.M, Chu D.K. Triple vs Dual Inhaler Therapy and Asthma Outcomes in Moderate to Severe Asthma: A Systematic Review and Meta-analysis.	JAMA - Journal of the American Medical Association 2021; 325:24 (2466-2479).

Source: Tables 22 & 23, pp48-51 of the submission; TRIMARAN CSR, TRIGGER CSR

6.8 The key features of the included evidence are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Treatment arms	Patient population	Key efficacy outcomes
BEC/FOR/GLY trials						
TRIMARAN	1,155	MC, R, OL, parallel, 2w run-in + 52w tx	Low	Medium dose ICS: BEC/FOR/GLY (100/6/10) BEC/FOR (100/6)	Aged 18-75y, Asthma, FEV1 <80%	Co-1º: Change in trough FEV1 (26w); rate of moderate/ severe exacerbations (52w). 2º: Change in peak 0-3h FEV1 (26w), change in PEF (26w), Proportion of FEV1 responders (26w & 52w), ACQ-7 (26w & 52w), rate of severe exacerbations (52w, pooled for TRIMARAN and TRIGGER).
TRIGGER	1,437	MC, R, OL[a], parallel, 2w run-in + 52w tx	High	High dose ICS: BEC/FOR/GLY (200/6/10) BEC/FOR+TIO (200/6 + 2.5) BEC/FOR (200/6)		
MF/IND/GLY trials						
IRIDIUM	3,092	MC, R, DB, parallel, 2w run-in + 52w tx	Low	Medium dose ICS: MF/IND/GLY (68/114/46) MF/IND (80/150) High dose ICS: MF/IND/GLY (136/114/46) MF/IND (160/150) FP/SAL (500/50)	Aged 18-75y, Asthma, FEV1 <80%	1º: Change in trough FEV1 (26w) 2º: ACQ-7 (26w), Other: Annualised rate of moderate/ severe exacerbations (52w), change in PEF (26w & 52w), ACQ-7 (52w), annualized rate of severe exacerbations, AQLQ (52w).
ARGON	1,426	MC, R, OL[b], parallel, 2w run-in + 24w tx	High	Medium dose ICS: MF/IND/GLY (68/114/46) High dose ICS: MF/IND/GLY (136/114/46) FP/SAL+TIO (500/50+5)	Aged ≥18y, Asthma, FEV1 <85%	1º: AQLQ (24w) 2º: Change in trough FEV1 (24w), ACQ-7 (24w), Other: rate of moderate/ severe exacerbations (24w), change in PEF, rate of severe exacerbations (24w).
FF/VI/UMEC trials						
CAPTAIN	2,439	MC, R, DB, parallel, 3w run-in + 2w stabilisation + 24w tx	Low	Medium dose ICS: FF/VI/UMEC (100/25/31.25) FF/VI/UMEC (100/25/62.5) FF/VI (100/25) High dose ICS: FF/VI/UMEC (200/25/31.25) FF/VI/UMEC (200/25/62.5) FF/VI (200/25)	Aged 18-75y, Asthma, FEV1 ≥30% and <85%	1º: Change in trough FEV1 (24w) 2º: Annualised rate of moderate/severe asthma exacerbations (24w, 52w), Other: Change in peak 0-3h FEV1 (24w), change in PEF, ACQ-7 (24w), annualised rate of severe exacerbations, AQLQ (24w).
Meta-analysis of ICS/LABA/LAMA vs. ICS/LAMA						
Rogliani 2021	9,535	RCTs of at least 24 weeks with at least one arm was triple combination ICS/LABA/LAMA therapy (5 trials: TRIMARAN, TRIGGER, IRIDIUM, ARGON & CAPTAIN); assessed change in trough FEV1 and rate of moderate/severe exacerbations. Secondary endpoint: ACQ.				
Kim 2021	11,894	RCTs of any duration comparing triple therapy (ICS/LABA/LAMA and ICS/LABA + LAMA) (20 studies, including TRIMARAN, TRIGGER, IRIDIUM, CAPTAIN PrimoTinA 1 & 2); assessments included change in trough FEV1 and rate of severe asthma exacerbations.				

Source: Tables 24, 25 & 33, pp55-60 & 82-83, pp61-62 & 84-89 of the submission, Kerstjens 2020, Gessner 2020, Lee 2021.

1º = primary; 2º = secondary; ACQ-7 = asthma control questionnaire, 7-item; AQLQ = asthma quality of life questionnaire; BEC = beclometasone dipropionate; Co-1º = co-primary; DB = double blind; FEV1 = forced expiratory volume in one second; FF = fluticasone furoate; FOR = formoterol fumarate; FP = fluticasone propionate; GLY = glycopyrronium; IND = indacaterol acetate; MF = mometasone fumarate; MC = multi-centre; OL = open label; PEF = peak expiratory flow; R = randomised; SAL = salmeterol; TIO = tiotropium; tx = treatment; VI=Vilanterol, UMEC = Umeclidinium; w = weeks.

[a] Partial blind/open-label study, BEC/FOR + TIO arm was open label. Therefore, the evaluation assessed the risk of bias to be high.

[b] Partial blind/open-label study, FP/SAL + TIO arm was open label. Therefore, the evaluation assessed the risk of bias to be high.

6.9 The tiotropium arms of the TRIGGER and ARGON trials were open label, which may be associated with potential treatment bias and detection bias. In the submission these

risks were marked as 'potential for bias' in the TRIGGER trial and 'moderate risk of bias' for the ARGON trial. The risk of bias was considered to be high for both trials. However, any bias is more likely to affect subjective outcomes, such as quality of life, rather than objective outcome, such as FEV1.

6.10 There were differences in the eligibility criteria and baseline patient characteristics across the trials (e.g., percentage of former smokers, mean duration of asthma, lung function):

- The percentage of former smokers was lower in the TRIMARAN and TRIGGER trials (range across arms: 13 to 16%) than the IRIDIUM and ARGON trials (19 to 24%). The CAPTAIN trial did not report the proportion of 'former' versus 'never' smokers.
- The mean duration of asthma varied from 16.8 years (IRIDIUM, MF/IND 160/150 µg arm) to 26.2 years (TRIGGER, BEC/FOR 200/6 µg arm).
- 37% of patients in the CAPTAIN trial had not had an exacerbation requiring oral corticosteroids or admission to hospital in the previous year, compared with <1% in all other trial arms.
- Participant lung function as a percentage of predicted varied across trials. Participants in the ARGON and CAPTAIN trials had better baseline lung function than participants in the TRIGGER, TRIMARAN, and IRIDIUM trials.
    - TRIMARAN: 51.8 to 52.1%
    - TRIGGER: 55.2 to 55.7%
    - IRIDIUM: 54.1 to 55.4%
    - ARGON: 62.2 to 63.4%
    - CAPTAIN: 67.2 to 69.6%

6.11 There was also a difference in the definition of asthma exacerbations across the trials:

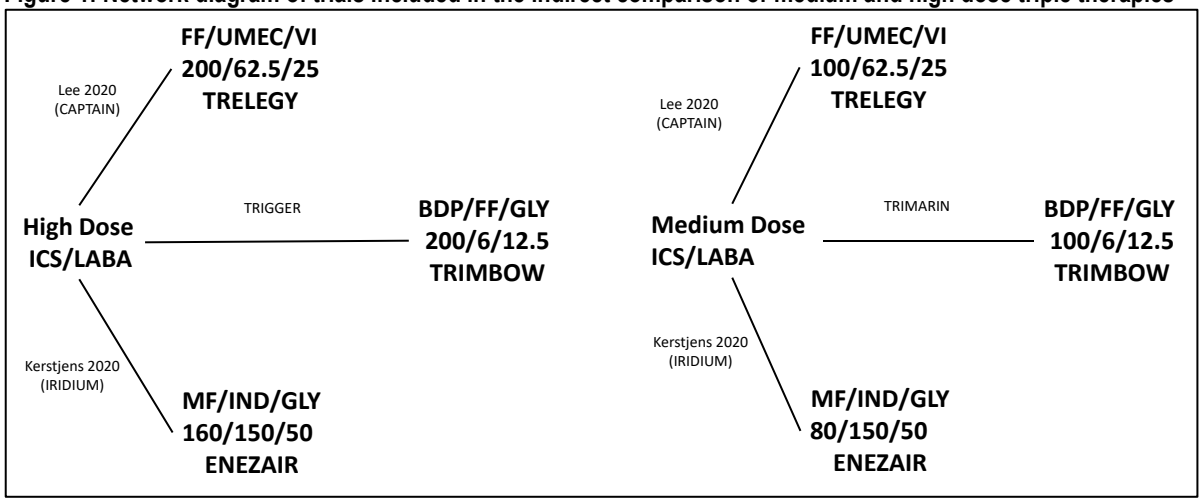
- Severe exacerbations: In the TRIMARAN and TRIGGER trials patients experiencing severe exacerbations received systemic corticosteroids, with any hospital visit documented. In the IRIDIUM and ARGON trials patients received systemic corticosteroids or were hospitalised due to asthma or died due to asthma. The definition of severe asthma exacerbation in the CAPTAIN trial was similar to the TRIMARAN and TRIGGER trials.
- Moderate exacerbations: The (increased) use of SABA and deterioration in FEV1 or FVC were common to all definitions. The TRIMARAN and TRIGGER trials included any hospital visit without receiving systemic corticosteroids. The CAPTAIN trial included exacerbations where a physician was needed to assess the patient and determined that additional therapy was warranted. The submission stated that physician involvement was not required to define a moderate exacerbation in the TRIMARAN and TRIGGER trials, where moderate exacerbations were higher.

These differences may affect the assumption of transitivity and thus the indirect comparison results.

6.12 The submission also presented four indirect treatment comparisons comparing medium dose and high dose BEC/FOR/GLY to medium dose and high dose

MF/IND/GLY and FF/VI/UMEC using any dual therapy as the common comparator. A network diagram of the trials included in the indirect comparison is presented in the figure below. The ARGON trial compared triple therapies only and thus did not allow for a common arm dual ICS/LABA comparison.

Figure 1: Network diagram of trials included in the indirect comparison of medium and high dose triple therapies



Source: Figure 21, p152 of the submission

BDP = beclometasone dipropionate (BEC in the ESC advice); FF= formoterol fumarate when in combination with beclometasone (FOR in the commentary); FF = fluticasone furoate when in combination with vilanterol (FF in the ESC advice); GLY = glycopyrronium; ICS = inhaled corticosteroid; IND = indacaterol; LABA = long-acting beta agonist; MF = mometasone fumarate; UMEC = umeclidinium; VI = vilanterol.

Notes: 1. 10 µg of glycopyrronium is equivalent to 12.5 µg glycopyrronium bromide. The BEC/FOR/GLY combinations shown above are equivalent to the proposed medium and high dose interventions (100/6/10 µg and 200/6/10 µg, respectively).

6.13 There were differences in the common reference across the trials (e.g., BEC/FOR versus FF/VI) that may affect the assumption of transitivity and thus the indirect comparison results.

Comparative effectiveness

Whole trial analysis

6.14 The results for change in trough FEV1 over 26 weeks in the TRIMARAN and TRIGGER trials are summarised in the table below.

Table 4: Results of change in trough FEV1 (L) across the included trials

	Medium dose BEC/FOR/GLY (100/6/10µg) N = 575				Medium dose BEC/FOR (100/6µg) N = 574				Mean difference (95% CI)	p value
TRIMARAN	Mean (SD) baseline (n = 575)	Mean (SD) week 26 (n = 557)	Mean (SD) change (n = 557)	Adj mean difference[a] (95% CI)	Mean (SD) baseline (n = 574)	Mean (SD) week 26 (n = 553)	Mean (SD) change (n = 553)	Adj mean difference[a] (95% CI)		
	1.869 (0.582)	2.059 (0.662)	0.186 (0.357)	0.185 (0.155; 0.214)	1.869 (0.594)	1.984 (0.679)	0.129 (0.369)	0.127 (0.098; 0.157)	**0.057 (0.015; 0.099)**	**0.008**
	High dose BEC/FOR/GLY (200/6/10µg) N = 571				**High dose BEC/FOR (200/6µg) N = 571**				**Mean difference (95% CI)**	**p value**
	Mean (SD) baseline (n = 570)	Mean (SD) week 26 (n = 552)	Mean (SD) change (n = 551)	Adj mean difference[a] (95% CI)	Mean (SD) baseline (n = 568)	Mean (SD) week 26 (n = 549)	Mean (SD) change (n = 547)	Adj mean difference[a] (95% CI)		
TRIGGER	1.746 (0.551)	1.979 (0.682)	0.227 (0.406)	0.229 (0.196; 0.263)	1.748 (0.567)	1.912 (0.687)	0.157 (0.387)	0.157 (0.123; 0.190)	**0.073 (0.026; 0.120)**	**0.003**
					High dose BEC/FOR + TIO (200/6 + 2.5µg) N = 287				**Mean difference (95% CI)**	**p value**
					Mean (SD) baseline (n = 287)	Mean (SD) week 26 (n = 275)	Mean (SD) change (n = 275)	Adj mean difference[a] (95% CI)		
					1.743 (0.570)	2.023 (0.741)	0.276 (0.436)	0.274 (0.227; 0.321)	-0.045 (-0.103; 0.013)	0.125

Source: Table 36, p96 of the submission.

BEC = beclometasone dipropionate; CI = confidence interval; FOR = formoterol fumarate; GLY = glycopyrronium; n = number of participants reporting data; N = total participants in group; SD = standard deviation; TIO = tiotropium.

[a] FEV1 was analysed using a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction and country as fixed effects, and baseline value and baseline by visit interaction as covariates

6.15 In both trials, the addition of GLY to BEC/FOR produced significant improvements in trough FEV1 over the 26-week treatment period when compared to BEC/FOR alone (p=0.008 and p=0.003 in the TRIMARAN and TRIGGER trials, respectively). There was no statistically significant difference between high dose BEC/FOR/GLY and BEC/FOR + TIO (p=0.125). None of these changes reach the minimal clinically important difference (MCID) of 100mL proposed in the submission.

6.16 The results for percentage of FEV1 responders (i.e., patients who achieved a change from baseline in pre-dose FEV1 ≥ 100mL) at 26 and 52 weeks in the TRIMARAN and TRIGGER trials are summarised in the table below.

Table 5: Results of FEV1 responders at 26 and 52 weeks across the included trials

TRIMARAN	**Week**	**Medium dose BEC/FOR/GLY (100/6/10µg) n/N (%)**	**Medium dose BEC/FOR (100/6µg) n/N (%)**	**Odds Ratio (95% CI)**	**p value**
	26	309/575 (53.7)	258/574 (44.9)	**1.439 (1.135; 1.824)**	**0.003**
	52	306/575 (53.2)	278/574 (48.4)	1.200 (0.944; 1.527)	0.137
TRIGGER	26	**High dose BEC/FOR/GLY (200/6/10µg) n/N (%)**	**High dose BEC/FOR (200/6µg) n/N (%)**	**Odds Ratio (95% CI)**	**p value**
		327/571 (57.3)	256/571 (44.8)	**1.656 (1.303; 2.104)**	**<0.001**
			High dose BEC/FOR + TIO (200/6 + 2.5µg) n/N (%)	**Odds Ratio (95% CI)**	**p value**
			174/287 (60.6)	0.844 (0.626; 1.139)	0.268
	52	**High dose BEC/FOR/GLY (200/6/10µg) n/N (%)**	**High dose BEC/FOR (200/6µg) n/N (%)**	**Odds Ratio (95% CI)**	**p value**
		325/571 (56.9)	240/571 (42.0)	**1.914 (1.499; 2.443)**	**<0.001**
			High dose BEC/FOR + TIO (200/6 + 2.5µg) n/N (%)	**Odds Ratio (95% CI)**	**p value**
			158/287 (55.1)	1.043 (0.770; 1.411)	0.787

Source: Table 41, pp111 of the submission.
BEC = beclometasone dipropionate; CI = confidence interval; FOR = formoterol fumarate; GLY = glycopyrronium; n = number of participants reporting data; N = total participants in group; SD = standard deviation; TIO = tiotropium.
Bold indicates statistically significant results.

6.17 In both trials the addition of GLY to BEC/FOR produced significant improvements in the proportion of FEV1 responders at 26 weeks when compared to BEC/FOR alone (p=0.003 and p<0.001 in the TRIMARAN and TRIGGER trials, respectively). However, at 52 weeks there was no significant difference between medium dose BEC/FOR/GLY and BEC/FOR (p=0.137). There was no statistically significant difference between high dose BEC/FOR/GLY and BEC/FOR + TIO (p=0.268). No MCID was proposed for this outcome.

6.18 The results for rate of moderate/severe asthma exacerbations in the TRIMARAN and TRIGGER trials are summarised in the table below.

Table 6: Results of annualised rate of moderate/severe asthma exacerbations across the included trials

	Medium dose BEC/FOR/GLY (100/6/10µg) N = 575				Medium dose BEC/FOR (100/6µg) N = 574				Adj. Rate ratio (95% CI)	p value
TRIMARAN	Patients (n, (%))	Exacerbations (n)	Annual rate	Adj. rate[a] (95% CI)	Patients (n, (%))	Exacerbations (n)	Annual rate	Adj. rate[a] (95% CI)		
	337 (59)	1,044	1.87	1.83 (1.63; 2.04)	379 (66)	1,215	2.19	2.16 (1.93; 2.40)	**0.85 (0.73; 0.99)**	**0.033**
	High dose BEC/FOR/GLY (200/6/10µg) N = 571				**High dose BEC/FOR (200/6µg) N = 571**				**Adj. Rate ratio (95% CI)**	**p value**
	Patients (n, (%))	Exacerbations (n)	Annual rate	Adj. rate[a] (95% CI)	Patients (n, (%))	Exacerbations (n)	Annual rate	Adj. rate[a] (95% CI)		
TRIGGER	323 (57)	990	1.79	1.73 (1.54; 1.93)	364 (64)	1,091	1.98	1.96 (1.76; 2.19)	0.88 (0.75; 1.03)	0.110
					High dose BEC/FOR + TIO (200/6 + 2.5µg) N = 287				**Adj. Rate Ratio (95% CI)**	**p value**
					Patients (n, (%))	Exacerbations (n)	Annualised rate	Adj. rate[a] (95% CI)		
					162 (56)	440	1.61	1.61 (1.37; 1.90)	1.07 (0.88; 1.30)	0.502

Source: Table 37, p102 of the submission.

BEC = beclometasone dipropionate; CI = confidence interval; FOR = formoterol fumarate; GLY = glycopyrronium; n = number of participants reporting data; N = total participants in group; SD = standard deviation; TIO = tiotropium.

[a] Rate of moderate/severe exacerbations was analysed using a negative binomial model including treatment, country, and number of exacerbations in the previous year (1 or > 1) as fixed effects, and log-time on study as an offset.

6.19 In the TRIMARAN trial the addition of GLY to medium dose BEC/FOR produced significant improvements in the adjusted rate of moderate/severe asthma exacerbations when compared to BEC/FOR alone (p=0.033). However, the improvement observed in the TRIGGER trial was not statistically significant (p=0.110). There was no statistically significant difference between high dose BEC/FOR/GLY and BEC/FOR + TIO (p=0.502). No MCID was proposed for this outcome.

6.20 The TGA Clinical Evaluation Report (Round 1) noted that the benefit of adding GLY to high dose BEC/FOR was not demonstrated as is requested by the TGA-adopted 'Guideline on clinical development of fixed combination medicinal products'. However, clinically relevant results for moderate and severe exacerbations were found in the pooled and post hoc analyses to support efficacy of the higher dose BEC/FOR/GLY product. The assessment and conclusions of the two Phase III clinical studies and the additional analyses by the EMA was found to be acceptable by the TGA clinical evaluator[3].

[3] pp7-8, TGA Clinical Evaluation Report, submission number PM-2021-0228-1-5

Meta-analyses

6.21 Rogliani (2021) performed a network meta-analysis based on phase III randomised controlled trials in asthma patients of at least 24 weeks duration and where at least one arm included a triple ICS-LABA-LAMA combination. This meta-analysis found that:

- High dose ICS/LABA/LAMA combinations (fixed dose combination as well as adding tiotropium to high dose ICS/LABA) were the most effective treatments in reducing the risk of moderate or severe asthma exacerbation, and more so than high dose ICS/LABA (relative risk (RR): 0.83; 95% CI: 0.69-1.00; p=0.05). Similarly, medium dose ICS/LABA/LAMA was more effective than medium dose ICS/LABA in preventing moderate-severe exacerbations (RR: 0.79; 95% CI: 0.65-0.94; p<0.05).
- High dose ICS/LABA/LAMA combinations were more effective than high dose ICS/LABA on change in trough FEV1 (relative effect: 72.6mL, 95% Credible Interval: 19.86, 126.45; p<0.05). Similarly, medium dose ICS/LABA/LAMA was more effective than medium dose ICS/LABA on change in trough FEV1 (relative effect: 81.49mL, 95% Credible Interval: 52.75, 110.76; p<0.05).
- Triple combination therapies were equally effective on asthma control, with no safety concerns. The meta-analysis by Rogliani (2021) did not conduct a non-inferiority analysis.

6.22 Kim (2021) performed a network meta-analysis based on clinical trials that were randomised, of any design and duration, comparing triple therapy (ICS/LABA, plus LAMA) with dual therapy (ICS plus LABA) in patients with moderate to severe asthma. This meta-analysis found that:

- Triple therapy was associated with an improvement in trough FEV1, with a mean difference of 0.08 L (95% CI: 0.07; 0.10; I2 = 0%, high certainty evidence).
- Triple therapy was significantly associated with a higher percentage of patients achieving a 200 mL increase from baseline compared with dual therapy (47% vs. 37%; RR = 1.27 [95% CI: 1.22; 1.32]).
- Triple therapy likely results in little to no difference in treatment-related adverse events (6.3% vs 5.3%; RR = 1.18 [95% CI: 0.96; 1.46]). Similar findings for any adverse event and serious adverse events. Triple therapy slightly increases dry mouth/dysphonia (3.0% vs. 1.8%; RR 1.65 [95%CI 1.14-2.38], high certainty).
- The results demonstrated no subgroup differences across 3 types of LAMAs in association with exacerbations, supporting a class effect. The meta-analysis by Kim (2021) did not conduct a non-inferiority analysis.

Indirect treatment comparison

6.23 The table below summarises the indirect treatment comparison results for change in trough FEV1 in millilitres (mL) over 26 weeks in the BEC/FOR/GLY trials (TRIMARAN

and TRIGGER) and MF/IND/GLY trial (IRIDIUM). The results for the FF/VI/UMEC trial (CAPTAIN) at 24 weeks are presented.

Table 7: Summary of results of the indirect comparison of change in trough FEV1 (mL): change from baseline to week 26 (TRIMARAN, TRIGGER & and IRIDIUM) or week 24 (CAPTAIN).

Comparison	Trial ID	ICS/LABA/LAMA Adjusted mean difference [a] (95% CI)	ICS/LABA Adjusted mean difference [a] (95% CI)	Treatment effect: mean difference (95% CI)	P value
Medium dose[b]					
BEC/FOR/GLY (100/6/10µg) vs. common reference	TRIMARAN	185 (155; 214)	127 (98; 157)	**57 (15; 99)**	**0.008**
MF/IND/GLY (68/114/46µg) vs. common reference	IRIDIUM	299	223	**76 (41; 111)**	**<0.001**
FF/VI/UMEC (100/25/62.5µg) vs. common reference	CAPTAIN	134 (104; 165)	24 (-6; 55)	**110 (66; 153)**	**<0.001**
Indirect estimate of effect BEC/FOR/GLY vs MF/IND/GLY [c]	–	–	–	-19 (-73.67; 35.67)	0.4958
High dose					
BEC/FOR/GLY (200/6/10µg) vs. common reference	TRIGGER	229 (196; 263)	157 (123; 190)	**73 (26; 120)**	**0.003**
MF/IND/GLY (136/114/46µg) vs. common reference	IRIDIUM	320	255	**65 (31; 99)**	**<0.001**
FF/VI/UMEC (200/25/62.5µg) vs. common reference	CAPTAIN	168 (137; 198)	76 (45; 106)	**92 (49; 135)**	**<0.0001**
Indirect estimate of effect BEC/FOR/GLY vs MF/IND/GLY [c]	–	–	–	8 (-66.01; 50.01)	0.7869
Indirect estimate of effect BEC/FOR/GLY vs FF/VI/UMEC [c]	–	–	–	-19 (-82.7; 44.7)	0.5588

Source: Tables 36, 44, 46, 57, 58, 67 & 68, pp96, 119, 121-123, 154 & 161-162 of the submission.

BEC = beclometasone dipropionate; CI = confidence interval; FF = fluticasone furoate; FOR = formoterol fumarate; GLY = glycopyrronium; ICS = inhaled corticosteroid; IND = indacaterol acetate; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; MF = mometasone fumarate; VI=Vilanterol, UMEC = Umeclidinium.

[a] In the TRIMARAN and TRIGGER trials, change in trough FEV1 was analysed using a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction and country as fixed effects, and baseline value and baseline by visit interaction as covariates. Similar adjustments were made in the IRIDIUM trial. The CAPTAIN trial used a similar model but also adjusted for sex, ICS dose at screening, and age.

[b] The submission noted that while medium dose FF/VI/UMEC has TGA approval for the asthma indication, it was not included in the submission considered by the PBAC in November 2021. No clinical claim was made in this submission against medium dose FF/VI/UMEC. The submission presented an indirect comparison against medium dose FF/VI/UMEC for completeness that is not included in the executive summary.

[c] The submission presented the indirect comparison with BEC/FOR/GLY as the comparator. The indirect comparison results presented in this table treat BEC/FOR/GLY as the intervention (i.e., the sign of the difference has been reversed).

6.24 The mean difference between medium dose BEC/FOR/GLY and MF/IND/GLY was -19 mL (95% CI: -73.97, 35.67; p=0.50). The mean difference between high dose BEC/FOR/GLY and MF/IND/GLY was 8 mL (95% CI: -66, 50; p=0.79). The mean difference between high dose BEC/FOR/GLY and FF/VI/UMEC was -19 mL (95% CI: -82, 45; p=0.56). The 95% CI for these comparisons remained within the MCID of 100 mL.

6.25 The table below summarises the indirect treatment comparison results for rate of moderate/severe asthma exacerbations. Annualised rates were calculated over 52

weeks for the TRIMARAN, TRIGGER, and IRIDIUM trials and 24 weeks for the CAPTAIN trial.

Table 8: Summary of results of the indirect comparison of annualised rate of moderate/severe asthma exacerbations over 52 weeks (TRIMARAN, TRIGGER, IRIDIUM) or 24 weeks (CAPTAIN).

Comparison	Trial ID	ICS/LABA/LAMA Adjusted rate [a] (95% CI)	ICS/LABA Adjusted rate [a] (95% CI)	Treatment effect: Rate ratio (95% CI)	P value
Medium dose[b]					
BEC/FOR/GLY (100/6/10µg) vs. common reference	TRIMARAN	1.83 (1.63; 2.04)	2.16 (1.93; 2.40)	**0.846 (0.725; 0.987)**	**0.033**
MF/IND/GLY (68/114/46µg) vs. common reference	IRIDIUM	0.58	0.67	0.87 (0.71; 1.06)	0.17
FF/VI/UMEC (100/25/62.5µg) vs. common reference	CAPTAIN	0.68 (0.56; 0.82)	0.87 (0.73; 1.04)	0.78 (0.61; 1.01)	0.060
Indirect estimate of effect BEC/FOR/GLY vs MF/IND/GLY [c]	–	–	–	0.97 (0.76; 1.25)	0.8283
High dose					
BEC/FOR/GLY (200/6/10µg) vs. common reference	TRIGGER	1.73 (1.54; 1.93)	1.96 (1.76; 2.19)	0.88 (0.751; 1.03)	0.110
MF/IND/GLY (136/114/46µg) vs. common reference	IRIDIUM	0.46	0.54	0.85 (0.68; 1.04)	0.12
FF/VI/UMEC (200/25/62.5µg) vs. common reference	CAPTAIN	0.55 (0.45; 0.67)	0.57 (0.47; 0.69)	0.97 (0.73; 1.28)	0.80
Indirect estimate of effect BEC/FOR/GLY vs MF/IND/GLY [c]	–	–	–	1.03 (0.79; 1.35)	0.7973
Indirect estimate of effect BEC/FOR/GLY vs FF/VI/UMEC [c]	–	–	–	0.90 (0.66; 1.25)	0.5536

Source: Tables 36, 44, 46, 63, 64, 71 & 72, pp96, 119, 121-123, 158-159 & 165 of the submission.

BEC = beclometasone dipropionate; CI = confidence interval; FF = fluticasone furoate; FOR = formoterol fumarate; GLY = glycopyrronium; ICS = inhaled corticosteroid; IND = indacaterol acetate; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; MF = mometasone fumarate; VI=Vilanterol, UMEC = Umeclidinium.

[a] In the TRIMARAN and TRIGGER trials, annualised rate of moderate/severe exacerbations was analysed using a negative binomial model including treatment, country, and number of exacerbations in the previous year (1 or > 1) as fixed effects, and log-time on study as an offset. The IRIDIUM and CAPTAIN trials both used generalised linear models assuming negative binomial distribution. No information regarding the IRIDUM model covariates was identified during the evaluation. The CAPTAIN model included covariates of treatment group, sex, region, pre-study ICS dosage at screening, age, and number of severe exacerbations in the previous year.

[b] The submission noted that while medium dose FF/VI/UMEC has TGA approval for the asthma indication, it was not included in the submission considered by the PBAC in November 2021. No clinical claim was made in this submission against medium dose FF/VI/UMEC. The submission presented an indirect comparison against medium dose FF/VI/UMEC for completeness that is not included in the executive summary.

[c] The submission presented the indirect comparison with BEC/FOR/GLY as the comparator. The indirect comparison results presented in this table treat BEC/FOR/GLY as the intervention (i.e., the ratio has been inverted).

6.26 When medium dose BEC/FOR/GLY was indirectly compared with medium dose MF/IND/GLY and FF/VI/UMEC, the indirect rate ratio was not statistically significant for either comparison. Similarly, the indirect rate ratios comparing high dose

BEC/FOR/GLY with high dose MF/IND/GLY and FF/VI/UMEC were not statistically significant.

6.27 The definition of 'moderate' and 'severe' asthma exacerbations varied across the TRIMARAN/TRIGGER, IRIDIUM, and CAPTAIN trials. These differences may have contributed to the differences in adjusted exacerbation rates observed in the common treatment arms (e.g., 2.16 for medium dose BEC/FOR versus 0.67 and 0.87 for medium dose MF/IND and FF/VI, respectively).

Comparative harms

6.28 The results of treatment exposure and safety outcomes in the TRIMARAN and TRIGGER trials are summarised in the table below.

Table 9: Summary of key adverse events in the included trials

Trial ID	TRIMARAN		TRIGGER		
Medicine	**Medium dose BEC/FOR/GLY (100/6/10µg)**	**Medium dose BEC/FOR (100/6µg)**	**High dose BEC/FOR/GLY (200/6/10µg)**	**High dose BEC/FOR (200/6µg)**	**High dose BEC/FOR + TIO (200/6 + 2.5µg)**
N	576	574	571	573	287
Completed treatment, n (%)[a]	424 (73.6)	408 (71.1)	412 (72.2)	406 (70.9)	217 (75.6)
Summary safety outcomes, n (%)					
TEAEs	431 (74.8)	455 (79.3)	410 (71.8)	443 (77.3)	210 (73.2)
Serious TEAEs	28 (4.9)	22 (3.8)	28 (4.9)	33 (5.8)	15 (5.2)
Drug related TEAEs	22 (3.8)	19 (3.3)	28 (4.9)	24 (4.2)	16 (5.6)
Serious drug related TEAEs	1 (0.2)	0 (0.0)	1 (0.2)	2 (0.3)	0 (0.0)
Severe TEAEs	34 (5.9)	38 (6.6)	35 (6.1)	55 (9.6)	13 (4.5)
TEAEs leading to study treatment discontinuation	4 (0.7)	5 (0.9)	4 (0.7)	8 (1.4)	2 (0.7)
TEAEs leading to death[b]	3 (0.5)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)
MACE[c]	4 (0.7)	1 (0.2)	3 (0.5)	3 (0.5)	0 (0)
TEAEs occurring in ≥3% patients, n (%)					
Asthma [exacerbation]	337 (58.5)	379 (66.0)	323 (56.6)	364 (63.5)	162 (56.4)
Nasopharyngitis	71 (12.3)	79 (13.8)	46 (8.1)	63 (11.0)	34 (11.8)
Headache	38 (6.6)	46 (8.0)	25 (4.4)	27 (4.7)	13 (4.5)
Respiratory tract infection viral	15 (2.6)	26 (4.5)	17 (3.0)	28 (4.9)	14 (4.9)
Bronchitis	18 (3.1)	22 (3.8)	18 (3.2)	18 (3.1)	12 (4.2)

Source: Tables 47-50, pp125,127-128 of the submission; Table 67, TRIMARAN CSR; Table 69, TRIGGER CSR.
BEC = beclometasone dipropionate; FOR = formoterol fumarate; GLY = glycopyrronium; MACE = major adverse cardiovascular events; n = number of participants reporting data; N = total participants in group; TEAEs = treatment emergent adverse events; TIO = tiotropium.
[a] Exposure results reported in table 47 of the submission and supported by the TRIMARAN and TRIGGER CSRs. Virchow reports 93.4%, 93.6%, 93.2%, 92.5%, and 91.0% patients in each arm completing treatment.
[b] none of the deaths were considered treatment related
[c] Added during the evaluation

6.29 In terms of treatment exposure, 89%, 95%, and 92% of patients completed treatment in the IRIDIUM, ARGON, and CAPTAIN trials, respectively.

6.30 The IRIDIUM trial presented safety results as incident rates per 100 patient-years (100 x number of patients with at least one event/time at risk for given adverse event in patient years), which complicates the comparison of this trial with the TRIMARAN, TRIGGER, ARGON, and CAPTAIN trials, which all present results as percentages.

6.31 The incident rate for adverse events in the IRIDIUM trial ranged between 163 to 194 events per 100 patient years across treatment arms. Across treatment arms in the ARGON trial, between 52% and 53% of patients experienced an adverse event. In the CAPTAIN trial, between 52% and 63% of patient experienced an adverse event.

6.32 The incident rate for serious adverse events in the IRIDIUM trial ranged between 7 and 9 events per 100 patient years. In the ARGON trial between 3% and 4% of patients in each arm experienced a serious adverse event. In the CAPTAIN trial between 4% and 6% of patients experienced a serious adverse event.

6.33 The incident rate for adverse events leading to study discontinuation in the IRIDIUM trial was between 2 and 4 per 100 patient years. In the ARGON trial 1% of patients experienced an adverse event leading to study discontinuation. In the CAPTAIN trial this ranged from <1% to 3% of patients across treatment arms.

6.34 The most common adverse events in the IRIDIUM and ARGON trials were asthma exacerbations (24-27% of patients in the ARGON trial), nasopharyngitis (7-9%), bronchitis (4-5%), upper respiratory tract infection (2-3%), headache (2-3%), and viral respiratory tract infection (2%), and pharyngitis (2-4%). The most common adverse events in the CAPTAIN trials were nasopharyngitis (13-15% of patients), headache (5-9%), upper respiratory tract infection (3-5%), bronchitis (3-5%), back pain (1-4%), viral respiratory tract infection (2-4%) influenza (1-3%), and pharyngitis (2-3%).

6.35 The incidence rate of major adverse cardiac events in the IRIDIUM trial was 1 per 100 patient years or fewer across treatment arms. Major adverse cardiac events were reported in fewer than 1% of patients in the ARGON and CAPTAIN trials.

6.36 Overall, the adverse event profile of BEC/FOR/GLY was similar to BEC/FOR and BEC/FOR + tiotropium in the TRIMARAN and TRIGGER trials. The adverse event profile of BEC/FOR/GLY also was similar to that of MF/IND/GLY in the IRIDIUM and ARGON trials and FF/VI/UMEC in the CAPTAIN trial.

Benefits/harms

6.37 There were no clinically meaningful differences between BEC/FOR/GLY and MF/IND/GLY and between BEC/FOR/GLY and FF/VI/UMEC, at corresponding doses of ICS, in efficacy and safety when used for the treatment of severe asthma.

Clinical claim

6.38 The submission described BEC/FOR/GLY (100/6/10 µg) as:

- Non inferior to MF/IND/GLY (68/114/46 µg) for both efficacy and safety, and
- Superior to BEC/FOR (100/6 µg) for efficacy and non-inferior in safety.

6.39 The submission described BEC/FOR/GLY (200/6/10 µg) as:

- Non inferior to MF/IND/GLY (136/114/46 µg) for both efficacy and safety,
- Non inferior to FF/VI/UMEC (200/25/62.5 µg) for both efficacy and safety,
- Non inferior to BEC/FOR + tiotropium (200/6 + 2.5 µg) for both efficacy and safety, and
- Superior to BEC/FOR (200/6 µg) for efficacy and non-inferior in safety.

6.40 The therapeutic conclusions presented in the submission for BEC/FOR/GLY compared to MF/IND/GLY and FF/VI/UMEC are uncertain because:

- No head-to-head trials comparing BEC/FOR/GLY, MF/IND/GLY, and FF/VI/UMEC were presented.
- The submission presented an indirect comparison using any dual therapy as the common comparator. Evidence was not presented to support this assumption, however the PBAC previously considered that a claim of non-inferior effectiveness and safety of BEC/FOR/GLY versus FF/VI/UMEC was reasonable for the COPD indication based on a similar assumption (paragraph 7.5, BEC/FOR/GLY, PSD, November 2020 PBAC meeting).
- There were differences in the eligibility criteria and baseline patient characteristics (e.g., percentage of former smokers, mean duration of asthma, lung function), the definition of asthma exacerbations, and the common reference (e.g., BEC/FOR versus FF/VI) across the trials that may affect the assumption of transitivity and thus the indirect comparison results.
- The submission nominated an MCID of 100 mL for change in trough FEV1, however no non-inferiority margin was nominated for moderate/severe asthma exacerbations, a co-primary endpoint in the TRIMARAN and TRIGGER trials. Differences in change in trough FEV1 for the indirect comparisons included in the clinical claim were not statistically significant and were within the nominated MCID. However, the upper 95% CIs for the indirect comparisons of the rate of moderate/severe asthma exacerbations (ranging between 1.25 and 1.35) were high and uncertain.

6.41 The therapeutic conclusions presented in the submission for BEC/FOR/GLY (200/6/10 µg) compared to BEC/FOR (200/6 µg) + tiotropium are uncertain because:

- The TRIGGER trial has a high risk of bias since the BEC/FOR + tiotropium arm was unblinded. However, any bias was more likely to affect subjective outcomes, such as asthma control, rather than objective outcomes, such as FEV1 and acute exacerbations.
- The submission nominated an MCID of 100 mL for change in trough FEV1. The submission did not nominate a non-inferiority margin for moderate/severe asthma exacerbations, a co-primary endpoint in the TRIGGER trial. A lack of statistical difference does not imply non-inferiority between interventions.

6.42 The therapeutic conclusions presented in the submission for BEC/FOR/GLY (100/6/10 µg) compared to BEC/FOR (100/6 µg) are reasonable because:

- BEC/FOR/GLY demonstrated a significant improvement in trough FEV1, and rate of moderate/severe asthma exacerbations compared to BEC/FOR (both primary outcomes in the TRIMARAN trial).
- Although the analysis of safety was only descriptive, the adverse event profiles appear similar.

6.43 The therapeutic conclusions presented in the submission for BEC/FOR/GLY (200/6/10 µg) compared to BEC/FOR (200/6 µg) are uncertain because:

- Although BEC/FOR/GLY demonstrated a significant improvement in trough FEV1, it did not demonstrate a significant improvement in rate of moderate/severe asthma exacerbations (one of two primary outcomes in the TRIGGER trial).
- Although the analysis of safety was only descriptive, the adverse event profiles appear similar.

6.44 Noting these uncertainties, the therapeutic conclusions may be reasonable, based on the two published meta-analyses (both of which considered triple vs dual combinations, not individual treatments) that conclude:

- Triple combination (ICS/LABA/LAMA) therapies were more effective than ICS/LABA therapies against moderate/severe exacerbation and increasing trough FEV1 (Rogliani 2021).
- Among adults with moderate to severe asthma, triple therapy, compared with dual therapy, was significantly associated with fewer severe asthma exacerbations and modest improvements in asthma control without significant differences in quality of life or mortality (Kim 2021).
- There were no subgroup differences across the three types of LAMA therapies in association with asthma exacerbations, supporting a class effect (Kim 2021).

6.45 The PBAC noted that in its November 2021 consideration of FF/VI/UMEC the committee had considered it was reasonable to rely predominantly on the primary outcome (FEV1) for the purposes of assessing non-inferiority (paragraph 7.5, FF/VI/UMEC PSD, November 2021 PBAC Meeting). The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.

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

Economic analysis

6.47 The cost-minimisation analysis was based on the claim of non-inferior effectiveness and safety for BEC/FOR/GLY compared to MF/IND/GLY at corresponding ICS strengths (medium and high dose). A cost-minimisation approach is consistent with the clinical claim.

6.48 The elements used to calculate equi-effective doses are presented in the table below.

Table 10: Elements used to calculate the equi-effective dose

Treatment	Dose/Day	Pack size	Days per pack	Treatment regimen
Medium dose				
BEC/FOR/GLY (100/6/10 µg)	Two actuations twice daily	120 doses	30	Chronic
MF/IND/GLY (68/114/46 µg)	One actuation daily	30 doses	30	
High dose				
BEC/FOR/GLY (200/6/10 µg)	Two actuations twice daily	120 doses	30	Chronic
MF/IND/GLY (136/114/46 µg)	One actuation daily	30 doses	30	

Source: p180 of the submission; BEC/FOR/GLY TGA product information; MF/IND/GLY TGA product information.
BEC = beclometasone dipropionate; FOR = formoterol fumarate; GLY = glycopyrronium; IND = indacaterol; MF = mometasone fumarate; TGA = Therapeutic Goods Administration.

6.49 The proposed equi-effective doses were consistent with the doses and treatment regimens in the TRIMARAN, TRIGGER, IRIDIUM and ARGON trials and the TGA Product Information for BEC/FOR/GLY and MF/IND/GLY.

6.50 The following additional cost comparisons were presented:

- Medium dose BEC/FOR/GLY (100/6/10 µg) to BEC/FOR + tiotropium (100/6 + 2.5 µg) and BEC + FOR + GLY as individual components (100 + 6 + 50 µg); and
- High dose BEC/FOR/GLY (200/6/10 µg) to BEC + FOR + GLY as individual components (200 + 6 + 50 µg).

6.51 The submission noted that while the components of BEC/FOR/GLY are individually listed on the PBS, the PBS listing for GLY is restricted to COPD and for a dose of 50 µg (five times the strength used in the triple combination therapy). Given there is no PBS listing for GLY (10 µg) as treatment for asthma, this cost comparison of BEC/FOR/GLY with its individual components was to provide context only.

6.52 The results of the cost-minimisation analysis for medium dose ICS are presented in the table below.

Table 11: Results of the cost-minimisation analysis – medium dose

Component	BEC/FOR/GLY (100/6/10 µg)	MF/IND/GLY (68/114/46 µg)	BEC/FOR + TIO (100/6 + 2.5 µg)		BEC + FOR + GLY (100 + 6 + 50 µg)		
PBS items	N/A	12298G	12183F & 11043F		8407L, 8239P & 10059K		
Actuations per day	4	1	4	2	4	4	1
Actuations per inhaler/pack	120	30	120	60	200	60	30
Days per pack	30	30	30	30	50	15	30
AEMP/pack	$[redacted]	$58.51	$29.69	$28.82	$17.77	$13.12	$44.95
Packs per year	[redacted]	12.175	12.175		7.305	24.35	12.175
Cost per year	$[redacted]	$712.36	$712.36		$996.55		
Difference in cost per year vs. BEC/FOR/GLY	N/A	[redacted]			$[redacted]		

Source: Table 78, p183 of the submission; BEC/FOR (100/6 µg) PI, tiotropium (2.5 µg) PI; glycopyrronium (50 µg) PI; November 2021 PBS.
AEMP = approved ex-manufacturer price; BEC = beclometasone dipropionate; FOR = formoterol fumarate; GLY = glycopyrronium; IND = indacaterol; MF = mometasone fumarate; N/A = not applicable; PBS = Pharmaceutical Benefits Scheme; PI = product information; TIO = tiotropium.

6.53 The results of the cost-minimisation analysis for high dose ICS are presented in the table below.

Table 12: Results of the cost-minimisation analysis – high dose

Component	BEC/FOR/GLY (200/6/10 µg)	MF/IND/GLY (136/114/46 µg)	BEC + FOR + GLY (100 + 6 + 50 µg)		
PBS items	N/A	12295D	8407L, 8239P & 10059K		
Actuations per day	4	1	8	4	1
Actuations per inhaler/pack	120	30	200	60	30
Days per pack	30	30	25	15	30
AEMP/pack	$	$74.01	$17.77	$13.12	$44.95
Packs per year		12.175	14.610	24.350	12.175
Cost per year	$	$901.07	$1,126.36		
Difference in cost per year vs. BEC/FOR/GLY	N/A				

Source: Table 78, p183 of the submission; glycopyrronium (50 µg) PI; November 2021 PBS.
AEMP = approved ex-manufacturer price; BEC = beclometasone dipropionate; FOR = formoterol fumarate; GLY = glycopyrronium; IND = indacaterol; MF = mometasone fumarate; N/A = not applicable.

6.54 There are multiple medium and high dose ICS/LABA combinations listed on the PBS which could be relevant comparators for the cost-minimisation analysis, when used in combination with tiotropium (2.5 µg) (see table below). Additional analyses conducted during the evaluation confirmed that the proposed costs of medium and high dose BEC/FOR/GLY were lower than or equal to that of other medium and high dose ICS/LABA combinations with tiotropium.

Table 13: Equi-potent ICS/LABA FDCs available on the PBS

	Medium dose ICS/LABA FDCs, providing 800 µg budesonide equi-potent per day for 30 days	High dose ICS/LABA FDCs, providing 1600 µg budesonide equi-potent per day for 30 days
DPI	FP/SAL 250/50 BD (Seretide® Accuhaler®; Fluticasone Salmeterol Ciphaler, Pavtide Accuhaler; 60) BUD/FOR 200/6 2 BD (Symbicort® Turbuhaler®, BiResp® Spiromax®, DuoResp® Spiromax®; 120) FF/VI 100/25 D (Breo® Ellipta®; 30)	FP/SAL 500/50 BD (Seretide® Accuhaler®, Pavtide Accuhaler; 60) BUD/FOR 400/12 2 BD (Symbicort® Turbuhaler®, BiResp® Spiromax®, DuoResp® Spiromax®; 120) FF/VI 200/25 D (Breo® Ellipta®; 30)
DPI caps	MF/IND 160/150 D (Atectura® Breezhaler®, 30)	MF/IND 320/150 D (Atectura® Breezhaler®; 30)
MDI	FP/SAL 125/25 2 BD (Seretide® MDI, Seroflo, SalplusF, Pavtide MDI, Fluticasone + Salmeterol Cipla, Evocair® MDI, 120) BUD/FOR 100/3 4 BD (Symbicort® Rapihaler®; 240) FP/FOR 125/5 2 BD (Flutiform®, 120) BEC/FOR 100/6 2 BD (Fostair®; 120)	FP/SAL 250/50 2 BD (Seretide® MDI, Seroflo, SalplusF, Pavtide MDI, Fluticasone + Salmeterol Cipla, Evocair® MDI; 120) BUD/FOR 200/6 4 BD (Symbicort® Rapihaler®; 240) FP/FOR 250/10 2 BD (Flutiform®; 120) -

Source: Table 8, MF/IND/GLY, PSD, July 2020 PBAC meeting, November 2021 PBS.
Abbreviations: BD=twice daily BEC=beclometasone; BUD=budesonide; D=once daily; DPI=dry powder inhaler; FF=fluticasone furoate; FOR=formoterol; FP=fluticasone propionate; IND=indacaterol; MDI=metered dose inhaler; MF=mometasone furoate; PBS = Pharmaceutical Benefits Scheme; SAL=salmeterol; VI=vilanterol.

6.55 The following ICS/LABA combinations are subject to price disclosure; therefore the outcome of the 2022 April price disclosure cycle may affect the lowest cost alternative for BEC/FOR/GLY: BUD/FOR and FP/SAL.

Drug cost/patient/course

6.56 The annual cost of medium dose BEC/FOR/GLY was $[redacted]. This calculation assumed 12.175 scripts per year at the requested DPMQ ($[redacted]). The estimated cost for the comparator, medium dose MF/IND/GLY, was $913.00.

6.57 The annual cost of high dose BEC/FOR/GLY was $[redacted]. This calculation assumed 12.175 scripts per year at the requested DPMQ ($[redacted]). The estimated cost for the comparator, high dose MF/IND/GLY, was $1,115.96.

Estimated PBS usage & financial implications

6.58 This submission was not considered by DUSC. The submission used a market share approach to estimate the utilisation and financial impacts associated with the PBS listing of BEC/FOR/GLY for severe asthma. This is reasonable. The key inputs used in the financial estimates are presented in the table below.

Table 14: Key inputs for financial estimates

Parameter	Value applied	Source	Comment
Market size			
Scripts in current market (ICS/LABA/LAMA)	MF/IND/GLY(MD): 200 MF/IND/GLY(HD): 531	Medicare Statistics PBS Item reports for 12298G, 12295D (Sep '20–Aug '21)	This is reasonable
Scripts in current market (ICS/LABA+ TIO)	317,500	Medicare Statistics PBS Item report for 11043F (Sep '20–Aug '21)	The number of TIO scripts dispensed for severe asthma was used to determine the ICS/LABA + LAMA market size.
Dual therapy market share	BUD/FOR: 37.67% FP/SAL: 45.27% FF/VI: 17.05%	Medicare Statistics PBS Item reports for 8625Y, 8750M, 10018G, 11273H, 11301T, 12082X, 12093L, 8431R, 8432T, 8518H, 8519J, 11124L, 11129R (Sep '20–Aug '21)	While the ICS/LABA + LAMA market size was determined by the number of TIO scripts dispensed, three ICS/LABA dual therapies were inappropriately excluded from the calculation of market share across ICS/LABA dual therapies (FP/FOR, MF/IND, BEC/FOR), with the impact on cost offsets unknown.
Medium versus high dose ICS/LABA market share	MD: 55.18% HD: 44.82%	Medicare Statistics PBS Item reports for 8625Y, 8750M, 10018G, 11273H, 11301T, 12082X, 12093L, 8431R, 8432T, 8518H, 8519J, 11124L, 11129R (Sep '20–Aug '21)	Three ICS/LABA dual therapies were inappropriately excluded from the analysis (FP/FOR, MF/IND, BEC/FOR) with the impact on the proportions reported unknown.
Market growth	2021: 4.5% 2022: 4.5% 2023: 4.0% 2024: 3.0% 2025: 2.5% 2026: 2.0%	Assumption	Market growth estimates were lower than those proposed in the MF/IND/GLY submission for severe asthma. The submission presented sensitivity analyses using the MF/IND/GLY market growth assumptions.
Treatment utilisation			
Uptake rate (from ICS/LABA/LAMA)	2022: 11.0% 2023: 22.0% 2024: 32.0% 2025: 34.5% 2026: 35.6%	Assumption	The first year of uptake estimates was 2022 (start month not specified), and not a full calendar year.

Parameter	Value applied	Source	Comment
	2027: 38.0%		
Uptake rate (from ICS/LABA + TIO)	2022: 29.0% 2023: 46.0% 2024: 56.0% 2025: 59.0% 2026: 62.0% 2027: 66.0%	Assumption	The first year of uptake estimates was 2022 (start month not specified), and not a full calendar year.
Conversion of ICS/LABA + TIO scripts to BEC/FOR/GLY	50% of ICS/LABA scripts offset, 50% of TIO scripts offset	Assumption	Linking BEC/FOR/GLY scripts to ICS/LABA scripts (including an adjustment for script equivalence) underestimates the number of BEC/FOR/GLY scripts (see paragraph 6.62)
Costs			
BEC/FOR/GLY (100/6/10 µg)	$[redacted]	Requested price, DPMQ	This is consistent with the cost-minimised price presented in the CMA.
BEC/FOR/GLY (200/6/10 µg)	$[redacted]	Requested price, DPMQ	
Patient copayment (Group 1 – tiotropium & BEC/FOR/GLY)	PBS: $9.90 RPBS: $3.97	Average copayment calculated based on PBS Item report for 11043F (Sep '20–Aug '21)	The approach is reasonable for TIO. The patient co-payments for BEC/FOR/GLY may be underestimated.
Patient copayment (Group 2 – MF/IND/GLY)	PBS: $18.80 RPBS: $1.76	Average copayment calculated based on PBS Item reports for 12298G, 12295D (Sep '20–Aug '21)	This is reasonable.
Patient copayment (Group 3 – ICS/LABA dual therapies)	PBS: $18.73 RPBS: $4.20	Average copayment calculated based on PBS Item reports for 8625Y, 8750M, 10018G, 11273H, 11301T, 12082X, 12093L, 8431R, 8432T, 8518H, 8519J, 11124L, 11129R (Sep '20–Aug '21)	Including these items is reasonable. Three ICS/LABA dual therapies were inappropriately excluded from the analysis (FP/FOR, MF/IND, BEC/FOR) with the impact on the patient copayment split reported unknown.

Source: Tables 79, 81, 82 & 84 pp185,187-189 of the submission; sheets '2e. Scripts – market' & '4b. Impact – affected (pub)' of the Section 4 workbook.

BEC = beclometasone dipropionate; BUD = budesonide; DPMQ = dispensed price for maximum quantity; FF = fluticasone furoate; FOR = formoterol fumarate; FP = fluticasone propionate; GLY = glycopyrronium; HD = high dose; ICS = inhaled corticosteroid; IND = indacaterol; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; MBS = Medicare Benefits Schedule; MD = medium dose; MF = mometasone fumarate; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; SAL = salmeterol; TIO = tiotropium; VI = vilanterol.

6.59 The estimated financial implications for the listing of medium and high dose BEC/FOR/GLY based on the prices cost minimised to MF/IND/GLY (DPMQs = $[redacted] and $[redacted], respectively) are presented in the table below.

Table 15: Estimated use and financial implications

	Year 1 2022	Year 2 2023	Year 3 2024	Year 4 2025	Year 5 2026	Year 6 2027
Estimated extent of use of BEC/FOR/GLY						
Number of BEC/FOR/GLY scripts dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
- Evaluation estimate[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated extent of use of MF/IND/GLY, TIO, BUD/FOR, FP/SAL and FF/VI						
Number of MF/IND/GLY scripts offset	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]
Number of TIO scripts offset	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]
Number of BUD/FOR scripts offset	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]
Number of FP/SAL scripts offset	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]
Number of FF/VI scripts offset	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]
Total scripts offset	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]
Estimated financial implications of BEC/FOR/GLY						
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
- Evaluation estimate[b]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for MF/IND/GLY, TIO, BUD/FOR, FP/SAL and FF/VI						
Cost to PBS/RPBS less copayments for MF/IND/GLY	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost to PBS/RPBS less copayments for TIO	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost to PBS/RPBS less copayments for BUD/FOR	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost to PBS/RPBS less copayments for FP/SAL	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost to PBS/RPBS less copayments for FF/VI	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Total cost offset	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net financial implications						
Net cost to PBS/RPBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
- Evaluation estimate[b]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to Government	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
- Evaluation estimate[b]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]

Source: Tables 85, 87, 89 & 91, pp190-191 & 193-194 of the submission; sheets '4a. Scripts – affected' & '4b. Impact – affected (pub)' of the Section 4 workbook.

BEC = beclometasone dipropionate; BUD = budesonide; FF = fluticasone furoate; FOR = formoterol fumarate; FP = fluticasone propionate; GLY = glycopyrronium; IND = indacaterol; MBS = Medicare Benefits Schedule; MF = mometasone fumarate; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; SAL = salmeterol; TIO = tiotropium; VI = vilanterol.

[a] Assuming 12.175 packs per year as estimated by the submission.

[b] BEC/FOR/GLY scripts calculated as 1:1 replacement of MF/IND/GLY and TIO scripts

The redacted values correspond to the following ranges
[1] *90,000 to < 100,000*
[2] *< 500*
[3] *30,000 to < 40,000*
[4] *40,000 to < 50,000*
[5] *10,000 to < 20,000*
[6] *100,000 to < 200,000*
[7] *$0 to < $10 million*
[8] *60,000 to < 70,000*
[9] *70,000 to < 80,000*
[10] *20,000 to < 30,000*
[11] *300,000 to < 400,000*
[12] *$10 million to < $20 million*
[13] *200,000 to < 300,000*
[14] *400,000 to < 500,000*
[15] *80,000 to < 90,000*
[16] *500,000 to < 600,000*

6.60 The total cost to the PBS/RPBS of listing BEC/FOR/GLY was estimated to be 10 million to < $20 million in Year 6, and a total of $80 million to < $90 million in the first 6 years of listing.

6.61 The submission stated that the net financial implications are cost savings, which results from reduced mark-ups and dispensing fees for one triple therapy versus an ICS/LABA plus tiotropium. The costs of various ICS/LABA + tiotropium combinations vary, and all dual + tiotropium combinations are currently more expensive than the only PBS-listed triple therapy (MF/IND/GLY). Since it is proposed that BEC/FOR/GLY be cost-minimised to MF/IND/GLY, a portion of the cost savings are associated with reduced utilisation of more expensive combination treatments.

6.62 The submission estimated the number of BEC/FOR/GLY scripts dispensed as a 1:1 replacement of MF/IND/GLY scripts and a 50:50 mixture of ICS/LABA and tiotropium scripts replaced, including a script equivalence ratio of 2:1 for two BUD/FOR PBS items with a 60-day treatment duration (10018G and 12082X). Where one BEC/FOR/GLY script (30 days) substitutes for one TIO script (30 days) and one BUD/FOR script (60 days), the rate of substitution will be every 30 days to maintain supply of the LAMA component. Estimating the number of BEC/FOR/GLY scripts based on 1:1 replacement of MF/IND/GLY and TIO scripts reduces the net cost savings to government over six years. The pre-PBAC response accepted the evaluation estimates proposed in Table 15.

6.63 The net financial impact to the R/PBS may be underestimated due to the potential for use of BEC/FOR/GLY in a less severe asthma population (i.e., patients currently receiving ICS/LABA treatment without tiotropium) and the potential for use of high dose BEC/FOR/GLY in the COPD indication (since only medium dose is listed for COPD).

Quality Use of Medicines

6.64 The submission stated that materials would be provided setting out the appropriate dosing for BEC/FOR/GLY in asthma and sales representatives, supported by a medical team, would visit treating centres to educate treating physicians and nurse practitioners on the approved dosing schedules for BEC/FOR/GLY in asthma.

6.65 BEC/FOR/GLY is administered as two actuations twice daily whereas MF/IND/GLY is administered as one actuation daily. The twice-daily dosing schedule may reduce compliance with BEC/FOR/GLY compared to MF/IND/GLY.

6.66 The quality use of medicines plan proposed does not consider the number and complexity of respiratory devices currently available in Australia, and the risk to consumers in terms of confusion regarding which inhalers to use when. As BEC/FOR/GLY is likely to replace multiple existing inhalers, a consumer education program may be required to ensure consumers are able to safely and adequately use the device. Similarly, health professional education beyond appropriate dosing may be required to ensure that health professionals are adequately skilled to support consumers in device use.

Financial Management – Risk Sharing Arrangements

6.67 The submission did not propose a risk-sharing arrangement.

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

7 PBAC Outcome

7.1 The PBAC deferred making a recommendation for the Authority Required (Streamlined) listing for a fixed dose combination (FDC) of beclometasone (BEC) with formoterol (FOR) and glycopyrronium (GLY) for the maintenance therapy of severe asthma as the TGA Delegate's Overview was not available at the time of consideration. However, the PBAC was of a mind to recommend the listing BEC/FOR/GLY for this indication based on its assessment that the cost of BEC/FOR/GLY should be no greater than the lowest price combination at approved ex-manufacturer price (AEMP) level of the PBS listed components of triple therapy that are available for asthma at comparable doses.

7.2 The PBAC noted the input from Asthma Australia supporting the listing of BEC/FOR/GLY for severe asthma.

7.3 The PBAC considered the nominated main comparator (mometasone with indacaterol and glycopyrronium (MF/IND/GLY)) and near market comparator (fluticasone furoate with vilanterol and umeclidinium (FF/VI/UMEC)) were appropriate. In addition, the PBAC considered that any medium and high dose inhaled corticosteroid (ICS) with long-acting beta agonist (LABA) plus long-acting muscarinic antagonist (LAMA) combination available for asthma could be considered appropriate alternative therapies to medium and high dose BEC/FOR/GLY, respectively.

7.4 To support the claim of non-inferior effectiveness, the submission presented indirect treatment comparisons comparing BEC/FOR/GLY to MF/IND/GLY and FF/VI/UMEC using the TRIMARAN, TRIGGER, IRIDIUM and CAPTAIN trials. The PBAC noted the transitivity concerns raised (see paragraphs 6.10 and 6.11), but considered the populations studied across the identified trials were broadly comparable. The PBAC noted that change in trough forced expiratory volume in 1 second (FEV1) and rate of

moderate/severe asthma exacerbations were the co-primary outcomes in the TRIMARAN and TRIGGER trials. The submission nominated a minimal clinically important difference (MCID) of 100 mL for change in trough FEV1, however no non-inferiority margin was nominated for the rate of moderate/severe asthma exacerbations. The PBAC noted that the differences in change in trough FEV1 for the indirect comparisons included in the clinical claim were not statistically significant and were within the nominated MCID. However, the upper 95% CIs for the indirect comparisons of the rate of moderate/severe asthma exacerbations (ranging between 1.25 and 1.35) were high and uncertain. The PBAC considered that it was reasonable, and consistent with previous recommendations, to rely predominantly on FEV1 in this context for the purposes of assessing non-inferiority (see paragraph 6.45). In addition, the PBAC considered that the results of the two published meta-analyses presented in the submission further supported the claim of non-inferior efficacy. Overall, the PBAC considered the claim of non-inferior effectiveness was reasonable.

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

7.6 The PBAC noted that the submission presented a cost-minimisation analysis between BEC/FOR/GLY and MF/IND/GLY. The PBAC accepted the equi-effective doses outlined in Table 10 as the basis for the analysis. However, the PBAC considered that the cost of BEC/FOR/GLY should be no greater than the lowest price combination at AEMP level of the PBS listed components of triple therapy that are available for asthma at comparable doses (see Table 10 and paragraph 6.54).

7.7 The PBAC noted the estimated use and financial implications of BEC/FOR/GLY and considered the approach taken by the evaluators as outlined in paragraph 6.62 appropriate.

7.8 The PBAC advised it would reconsider BEC/FOR/GLY at its next available opportunity following provision of the TGA Delegate's Overview to make a recommendation regarding listing on the PBS.

Outcome:
Deferred

Addendum to the March 2022 PBAC Public Summary Document:

8 Background

8.1 At its March 2022 meeting, the PBAC deferred making a recommendation for the Authority Required (Streamlined) listing for a fixed dose combination (FDC) of beclometasone (BEC) with formoterol (FOR) and glycopyrronium (GLY) for the maintenance therapy of severe asthma as the TGA Delegate's Overview was not available at the time of consideration. However, the PBAC was of a mind to recommend the listing BEC/FOR/GLY for this indication based on its assessment that the cost of BEC/FOR/GLY should be no greater than the lowest price combination at approved ex-manufacturer price (AEMP) level of the PBS listed components of triple therapy that are available for asthma at comparable doses.

8.2 The sponsor provided the positive TGA Delegate's Overview on 6 April 2022.

9 PBAC Outcome

9.1 The PBAC recommended the Authority Required (Streamlined) listing for a fixed dose combination (FDC) of beclometasone (BEC) with formoterol (FOR) and glycopyrronium (GLY) for the maintenance therapy of severe asthma. Noting the TGA Delegate supported registration of BEC/FOR/GLY for this indication, the PBAC was satisfied the remaining outstanding issues relating to the application were satisfactorily resolved.

9.2 The PBAC considered the claim of non-inferior effectiveness and safety to the FDC of mometasone with indacaterol and glycopyrronium (MF/IND/GLY) was reasonable. However, the PBAC considered for purposes of satisfying Section 101(3B) of the *National Health Act 1953*, any medium and high dose inhaled corticosteroid (ICS) with long-acting beta agonist (LABA) plus long-acting muscarinic antagonist (LAMA) combination available for asthma are relevant alternative therapies. The PBAC's recommendation was therefore, among other matters, based on its assessment that the cost of BEC/FOR/GLY should be no greater than the lowest price combination at approved ex-manufacturer price (AEMP) level of the PBS listed components of triple therapy that are available for asthma at comparable doses.

9.3 The PBAC advised that BEC/FOR/GLY is suitable for prescribing by nurse practitioners.

9.4 The PBAC recommended that the Early Supply Rule should apply.

9.5 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because BEC/FOR/GLY is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over MF/IND/GLY, 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.

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

Outcome:
Recommended

10 Recommended listing

Add new indication of severe asthma (18274) to the current BEC/FOR/GLY 100µg/6µg/10µg PBS listing (12468F) as follows:

MEDICINAL PRODUCT medicinal product pack		PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
BECLOMETASONE + FORMOTEROL (EFORMOTEROL)+ GLYCOPYRRONIUM						
Beclometasone dipropionate 100 microgram/actuation + formoterol (eformoterol) fumarate 6 microgram/actuation + glycopyrronium 10 microgram/actuation inhalation, 120 actuations		12468F	1	1	5	Trimbow
Restriction Summary: [11470] / Treatment of Concept: [11470] – Copied from Enerzair Breezhaler's Restriction for severe asthma						
	Category / Program: GENERAL – General Schedule (Code GE)					
	Prescriber type: ☒Medical Practitioners ☒Nurse practitioners					
	Restriction type: ☒Authority Required (Streamlined) [new/existing code]					
	Indication: Severe asthma					
	Clinical criteria:					
	Patient must have experienced at least one severe asthma exacerbation in the 12 months prior to having first commenced treatment for severe asthma, which required systemic corticosteroid treatment despite each of: (i) receiving optimised asthma therapy, (ii) being assessed for adherence to therapy, (iii) being assessed for correct inhaler technique.					
	Population criteria:					
	Patient must be aged 18 years or over					
	Prescribing Instructions: Optimised asthma therapy includes adherence to the maintenance combination of an inhaled corticosteroid (at least 800 micrograms budesonide per day or equivalent) and a long acting beta-2 agonist.					
	Administrative Advice: Formal assessment and correction of inhaler technique should be performed in accordance with the National Asthma Council (NAC) Information Paper for Health Professionals on Inhaler Technique (available at www.nationalasthma.org.au); the assessment and adherence to correct technique should be documented in the patient's medical records. Patients can obtain support with inhaler technique through their local Asthma Foundation (1800 645 130).					
	Administrative Advice: This product is not indicated for the initiation of treatment in asthma					
	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.					

No changes will be made to the current PBS listing for the indication of COPD (9286), reproduced below:

Restriction Summary: [12349] / Treatment of Concept: [12349]	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners ☒Nurse practitioners
	Restriction type: ☒Authority Required (Streamlined) [new/existing code]
	Indication: Chronic obstructive pulmonary disease (COPD)
	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
	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: An ICS includes fluticasone propionate, fluticasone furoate, budesonide, beclometasone or ciclesonide.
	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.

Add new medicinal product pack (new strength: 200 µg/6µg/10µg) for the indication of severe asthma (18274) as follows:

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
BECLOMETASONE + FORMOTEROL (EFORMOTEROL)+ GLYCOPYRRONIUM					
Beclometasone dipropionate 200 microgram/actuation + formoterol (eformoterol) fumarate 6 microgram/actuation + glycopyrronium 10 microgram/actuation inhalation, 120 actuations	NEW	1	1	5	Trimbow
Restriction Summary: New/ Treatment of Concept: New – based on Enerzair Breezhaler's Restriction for severe asthma					
	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: ☒Medical Practitioners ☒Nurse practitioners				
	Restriction type: ☒Authority Required (Streamlined) [new/existing code]				
	Indication: Severe asthma				
	Clinical criteria:				
	Patient must have experienced at least one severe asthma exacerbation in the 12 months prior to having first commenced treatment for severe asthma, which required systemic corticosteroid treatment despite each of: (i) receiving optimised asthma therapy, (ii) being assessed for adherence to therapy, (iii) being assessed for correct inhaler technique.				

	Population criteria:
	Patient must be aged 18 years or over
	Prescribing Instructions: Optimised asthma therapy includes adherence to the maintenance combination of an inhaled corticosteroid (at least 800 micrograms budesonide per day or equivalent) and a long acting beta-2 agonist.
	Administrative Advice: Formal assessment and correction of inhaler technique should be performed in accordance with the National Asthma Council (NAC) Information Paper for Health Professionals on Inhaler Technique (available at www.nationalasthma.org.au); the assessment and adherence to correct technique should be documented in the patient's medical records. Patients can obtain support with inhaler technique through their local Asthma Foundation (1800 645 130).
	Administrative Advice: This product is not indicated for the initiation of treatment in asthma
	Administrative Advice: This pharmaceutical benefit is not for the treatment of chronic obstructive pulmonary disease
	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.

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

11 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.

12 Sponsor's Comment

Chiesi Australia is pleased with the PBAC recommendation of TRIMBOW for the treatment of severe asthma. This offers Australian asthma suffers with an alternative and convenient triple therapy.