5.29 FLUTICASONE FUROATE with UMECLIDINIUM and VILANTEROL,
Powder for oral inhalation in breath actuated device containing fluticasone furoate 200 micrograms with umeclidinium 62.5 micrograms (as bromide) and vilanterol 25 micrograms (as trifenatate) per dose, 30 doses,
Trelegy® Ellipta® 200/62.5/25,
GlaxoSmithKline Australia Pty Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested an Authority Required (Streamlined) listing for Trelegy® Ellipta®, a fixed dose combination (FDC) of fluticasone furoate (FF), an inhaled corticosteroid (ICS) with umeclidinium (UMEC), a long-acting muscarinic antagonist (LAMA), and vilanterol (VI), a long-acting beta2 agonist (LABA) for maintenance therapy of severe asthma (hereafter FF/UMEC/VI).

1.2 The proposed listing is for one strength: FF/UMEC/VI 200/62.5/25 mcg. The submission noted that the FF/UMEC/VI dosing would be equivalent to >800 mcg budesonide equi-potent per day and hence is considered a 'high' dose ICS product in line with Australian guidelines.

1.3 Mometasone furoate (MF)/indacaterol (IND)/glycopyrronium (GLY) (hereafter MF/IND/GLY) is PBS listed to treat severe asthma. The MF/IND/GLY inhaler requires capsules to be loaded by the patient prior to use. In contrast, FF/UMEC/VI is a dry powder inhalation (DPI) device (Ellipta), which has a single step activation procedure of "Open - Inhale - Close".

1.4 Listing of FF/UMEC/VI 200/62.5/25 was requested on the basis of a cost-minimisation analysis versus MF/IND/GLY 136/114/46 or high dose ICS/LABAs + tiotropium (TIO).

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

Component	Description
Population	Asthma patients who are currently uncontrolled on ICS/LABA treatments
Intervention	FF/UMEC/VI, a once-daily dry powder inhaler containing fluticasone furoate (FF), umeclidinium bromide (UMEC) and vilanterol trifenatate (VI), 200/62.5/25 mcg per actuation
Comparator	Single inhaler triple therapy including Enerzair® Breezhaler® (MF/IND/GLY) 136/114/46 mcg, OR Multiple inhaler triple therapy containing high[a] dose ICS/LABA FDCs plus TIO[b] Clinical evidence presented informs the following comparisons: •FF/UMEC/VI 200/62.5/25 mcg one actuation once daily versus MF/IND/GLY 136/114/46 mcg, one actuation once daily via indirect treatment comparison •FF/UMEC/VI 200/62.5/25 mcg one actuation once daily versus high dose ICS/LABA + TIO 2.5 mcg two actuations once daily via indirect treatment comparison
Outcomes	Efficacy: Trough FEV1; annualised rate of moderate/severe exacerbations; time to first moderate/severe exacerbation, ACQ-7 total score; ACQ-7 responder rate; AQLQ total score Safety: Frequency of any adverse events (AEs), serious AEs (SAEs), AEs that were frequently reported (occurring in ≥3% of subjects in either treatment arm) and AEs of special interest
Clinical claim	In adults with asthma who remain uncontrolled on ICS/LABA: FF/UMEC/VI 200/62.5/25 is non-inferior to MF/IND/GLY 136/114/46 as well as high dose ICS/LABA+TIO in terms of the primary outcome of Trough FEV1 FF/UMEC/VI 200/62.5/25 has similar or comparable safety compared with MF/IND/GLY 136/114/46 as well as high dose ICS/LABA

Source: Table 1, p16 of the submission.

ACQ-7: Asthma Control Questionnaire; AE: adverse event; AQLQ: Asthma Quality of Life Questionnaire; FDC: fixed dose combination; FEV1: forced expiratory volume in one second; FF: fluticasone furoate; GLY: glycopyrronium; ICS: inhaled corticosteroid; IND: indacaterol; LABA: long-acting beta2-adrenergic agonist; LAMA: long-acting muscarinic receptor antagonist; MF: mometasone furoate; SAE: serious adverse event; TIO: tiotropium; UMEC: umeclidinium VI: vilanterol

[a] High dose (i.e. providing >800 mcg budesonide equi-potent per day) ICS/LABA FDCs for asthma include:
Fluticasone propionate (FP)/ Salmeterol 500/50 mcg one actuation twice daily (Seretide® Accuhaler®)
FP/SAL 250/25 mcg two actuations twice daily (Seretide® Evocair®, Fluticasone + Salmeterol Cipla®, SalPlusF®, Seroflo®, Pavtide®)
Budesonide (BUD)/ Formoterol (FOR) 400/12 mcg two actuations twice daily (Symbicort® Turbuhaler®, Duoresp® Spiromax®)
BUD/FOR 200/6 mcg four actuations twice daily (Symbicort® Rapihaler®)
FP/FOR 250/10 mcg two actuations twice daily (Flutiform®)
Fluticasone furoate (FF)/Vilanterol (VI) 200/25 mcg one actuation daily (Breo® Ellipta®)
Mometasone furoate (MF)/Indacaterol (IND) 320/150 mcg one actuation daily (Atectura® Breezhaler®). The submission reported the dosage for MF/IND to be 260/125 mcg, however the TGA recommended the dosage to be reported as 320/150 mcg (delivered dose 260 mcg MF, 125 mcg IND) (paragraph 2.40, MF/IND Public Summary Document (PSD), July 2020 PBAC Meeting).

[b] TIO 2.5 mcg two inhalations once daily (Spiriva® Respimat®) is the only PBS-listed LAMA to treat asthma.

2 Background

Registration status

2.1 FF/UMEC/VI received Therapeutic Goods Administration (TGA) registration on 10 May 2021 for the maintenance treatment of asthma in adult patients who are not adequately controlled with a combination of ICS and a LABA.

2.2 The TGA approved two strengths of FF/UMEC/VI (100/62.5/25 and 200/62.5/25) for asthma, but a PBS listing was requested for only FF/UMEC/VI 200/62.5/25 (high dose). The submission considered that the use of FF/UMEC/VI 100/62.5/25 for asthma should be in a different population to that allowed by the current PBS restriction. The FF/UMEC/VI 100/62.5/25 product is currently PBS-listed for the maintenance treatment of adults with moderate to severe COPD who require treatment with LAMA

+ ICS + LABA. The FF/UMEC/VI 200/62.5/25 product is not PBS listed for COPD and there is a chance of use beyond the intended severe asthma population to people with COPD alone.

2.3 The submission reported that FF/UMEC/VI 200/62.5/25 mcg received approval for the maintenance treatment of asthma in the USA (September 2020), Japan (November 2020) and Canada (May 2021). However, the European Union's healthcare regulator, the European Medicines Agency[1], did not approve FF/UMEC/VI to treat asthma as it considered that an improvement in lung function (i.e., change in FEV1 after 24 weeks of treatment) alone is not enough to show that a medicine is suitable for treating asthma. Further, the agency considered that the pivotal trial (CAPTAIN) did not clearly show that the medicine was effective at reducing asthma attacks or controlling symptoms.

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.

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Dispensed price for maximum quantity**	**Available brands**
FLUTICASONE FUROATE + UMECLIDINIUM + VILANTEROL						
fluticasone furoate 200 microgram/actuation + umeclidinium 62.5 microgram/actuation + vilanterol 25 microgram/actuation powder for inhalation, 30 actuations	NEW	1	30	5	$91.60	Trelegy Ellipta
Restriction Summary [11470] / Treatment of Concept: [11470] *(based on Enerzair Breezhaler's restriction as at 1 September 2021)*						
Category / Program: GENERAL – General Schedule (Code GE)						
Prescriber type: ☒Medical Practitioners ☒Nurse practitioners						
Restriction type: ☒~~Authority Required (Streamlined) [new/existing code]~~ ☒*Authority Required (telephone/online PBS Authorities system)*						
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						
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:						

[1] Source: https://www.ema.europa.eu/en/documents/smop/questions-answers-refusal-change-marketing-authorisation-trelegy-ellipta-fluticasone-furoate/umeclidinium/vilanterol_en.pdf

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 drug is not PBS-subsidised for the treatment of chronic obstructive pulmonary disease (COPD)~~
Administrative Advice: *This pharmaceutical benefit is not for the treatment of chronic obstructive pulmonary disease (COPD)*
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.
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.

3.2 The submission requested an Authority Required (STREAMLINED) listing for FF/UMEC/VI 200/62.5/25. A more restrictive Authority Required listing (telephone/online) was applied for MF/IND/GLY, the main comparator in the current submission, with the rationale being that it would aid in minimising the risk of inappropriate use in patients with less severe asthma otherwise managed on ICS or ICS/LABA (paragraphs 7.8 and 9.3, MF/IND/GLY Public Summary Document (PSD), July 2020 PBAC Meeting).

3.3 In the July 2020 consideration of MF/IND/GLY it was noted that it could be inappropriately prescribed in children and adolescents, given triple therapy with ICS/LABA+TIO is PBS listed from 6 years of age, but listing of MF/IND/GLY was sought for adults. At that time, the PBAC considered that patient age confirmation as part of an Authority Required (telephone/online) application process may assist in minimising this potential quality use of medicines issue (paragraph 6.44, MF/IND/GLY PSD, July 2020 PBAC Meeting). The evaluation considered there exists a similar concern regarding the use of FF/UMEC/VI 200/62.5/25 among patients less than 18 years. The Pre-Sub-Committee Response (PSCR) contended that the authority type (telephone/online) applied to MF/IND/GLY was likely a barrier to prescribing as Medicare Statistics prescribing data for the first 4 months of listing suggested uptake was lower than expected in the July 2020 submission. The ESC considered the concerns regarding the risk of inappropriate use raised by the PBAC in July 2020 for MF/IND/GLY were applicable to FF/UMEC/VI. The pre-PBAC response further contended that patients and clinicians should not have inconsistent treatment restrictions to prescribing when STREAMLINED Authorities have managed appropriate prescribing of ICS/LABAs and ICS/LABA/LAMA single inhaler triple therapy prescribing elsewhere in the management of respiratory conditions. The PBAC noted the differences in the restriction types for tiotropium (Restricted Benefit for severe asthma), FF/UMEC/VI 100/62.5/25 mcg (Authority Required - STREAMLINED for COPD) and MF/IND/GLY (Authority Required – telephone/online for severe asthma).

The PBAC agreed with the pre-PBAC response that the inconsistencies evident between the single inhaler triple therapies across these two indications may not be appropriate.

3.4 The requested restriction is consistent with that of the current MF/IND/GLY listing for severe asthma. The PSCR noted a proposed correction to the clinical criteria of the MF/IND/GLY listing highlighted by the Secretariat. The correction clarified that continuing patients need not re-experience severe exacerbations on a recurring 12-month basis to qualify for continued treatment. The PSCR was accepting of the proposal by the Secretariat to apply the same correction to the proposed FF/UMEC/VI clinical criterion which would now state:

> 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.

3.5 FF/UMEC/VI 100/62.5/25 mcg is currently PBS-listed for the maintenance treatment of adults with moderate to severe COPD who require treatment with LAMA + ICS + LABA. Although the "administrative advice" of the requested restriction for the 200/62.5/25 mcg dosage noted that "this drug strength is not PBS-subsidised for the treatment of chronic obstructive pulmonary disease (COPD)", the ESC considered there is a chance of use in COPD patients who do not have asthma.

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. A stepwise approach involves the adjustment of medication up or down to achieve good symptom control and minimise future risk of exacerbations and medication side-effects. A targeted approach for severe asthma is aimed at eliminating symptoms and exacerbation risks. 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 or high dose ICS/LABA can be prescribed ICS/LABA/LAMA

treatment. In the Australian and international guidelines, medium dose ICS includes 800 mcg of budesonide per day or equivalent (at the upper dosage limit), and high dose ICS refers to more than 800 mcg of budesonide per day or equivalent.

4.3 The submission proposed that FF/UMEC/VI 200/62.5/25 would be an alternative treatment option to high dose ICS/LABA+LAMA (i.e., high dose ICS/LABA + TIO) or to MF/IND/GLY 136/114/46 (Step 4 in the Australian Asthma Handbook (AAH) stepwise treatment algorithm). MF/IND/GLY 136/114/46 was proposed as an alternative treatment option to add on LAMA (i.e. TIO) in 'add-on specialised treatment' (Step 5) for patients with uncontrolled asthma taking moderate (i.e. medium) or high dose ICS/LABA (paragraph 4.3, MF/IND/GLY PSD, July 2020 PBAC Meeting). There is some overlap between Step 4 and Step 5 of the treatment algorithm[2] as the Australian guidelines state that adults with confirmed severe asthma who continue to experience frequent symptoms or flare-ups despite optimisation of inhaler technique and adherence, and treatment of comorbidities, a trial of add-on treatment with TIO or montelukast can be considered in primary care before referring for specialist assessment for monoclonal antibody therapy (paragraph 4.3, MF/IND/GLY PSD, July 2020 PBAC Meeting).

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

5 Comparator

5.1 The submission nominated MF/IND/GLY 136/114/46 and high dose ICS/LABA FDCs + TIO as the comparators. MF/IND/GLY 136/114/46 was nominated as the main comparator.

5.2 While both medium and high dose ICS/LABA+TIO would be potential comparators, the submission chose only high dose ICS/LABA+TIO because FF/UMEC/VI 200/62.5/25 mcg contains the equivalent high dose ICS (i.e., FF 200 mcg). Consistent with this the PSD for MF/IND/GLY noted that "the nominated comparison between medium dose MF/IND/GLY versus high dose ICS/LABA + LAMA … may not be clinically appropriate. In practice, medium dose MF/IND/GLY may substitute for medium dose ICS/LABA FDC + LAMA given symptomatic patients taking optimised medium dose ICS/LABA are eligible for triple therapy on the PBS. Patients are likely to step up from optimised medium dose ICS/LABA to medium dose ICS/LABA/LAMA without concurrently changing the dose of ICS" (paragraph 5.2, MF/IND/GLY PSD, July 2020 PBAC Meeting).

5.3 The submission noted that the Global Initiative for Asthma (GINA) guidelines recommend montelukast (GINA step 4) as an add-on to medium dose ICS/LABA. Further, it mentioned that several biologics, including mepolizumab, reslizumab,

[2] https://www.asthmahandbook.org.au/static/files/Australian-Asthma-Handbook-v2.0-Management-%E2%80%93-Adults.pdf

benralizumab, dupilumab and omalizumab have been approved by both the European Medicines Agency and Food and Drug Administration for the treatment of severe persistent asthma (GINA step 5) (p27 of the submission). However, the AAH treatment guidelines do not recommend montelukast and it is only PBS-approved for use in pediatric, exercise-induced asthma. Further, the use of the biological agents is limited to patients with very severe asthma (step 5 of AAH guidelines) (Figure 1.2.2, Attachment 1). Thus, both montelukast and biologics were not proposed as potential comparators for FF/UMEC/VI 200/62.5/25. The evaluation considered this was reasonable.

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 health care professionals (1) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with FF/UMEC/VI including that single inhaler triple therapy provides a treatment option for ICS/LAMA/LABA therapy that is likely less costly and more convenient than mixing device types. In addition, the comments highlighted concerns that the PBS process for obtaining authority for single agent triple therapy for asthma will be unnecessarily complex and time consuming compared to single inhaler triple therapy for conditions such as COPD.

Clinical trials

6.3 The submission was based on one randomised trial comparing FF/UMEC/VI to dual therapy: CAPTAIN. In addition it presented five randomised trials:

- Two comparing high dose single inhaler triple therapy (beclometasone dipropionate/formoterol/glycopyrronium (BDP/FOR/GLY)) and high dose ICS/LABA (BDP/FOR or MF/IND or FP/SAL): TRIGGER, IRIDIUM.
- Two comparing high dose single inhaler triple therapy (BDP/FOR/GLY or MF/IND/GLY) and high dose multiple inhaler triple therapy (BDP/FOR + TIO or FP/SAL + TIO): TRIGGER and ARGON.
- Two (based on the trials PrimoTinA 1 & 2) comparing pooled medium/high dose multiple inhaler triple therapy (ICS/LABA + TIO) and pooled medium/high dose ICS/LABA (PrimoTinA 1 & 2).

6.4 The PBAC considered the ARGON and IRIDIUM trials during the assessment of MF/IND/GLY in July 2020. The submission for MF/IND/GLY also presented evidence from the CAPTAIN trial.

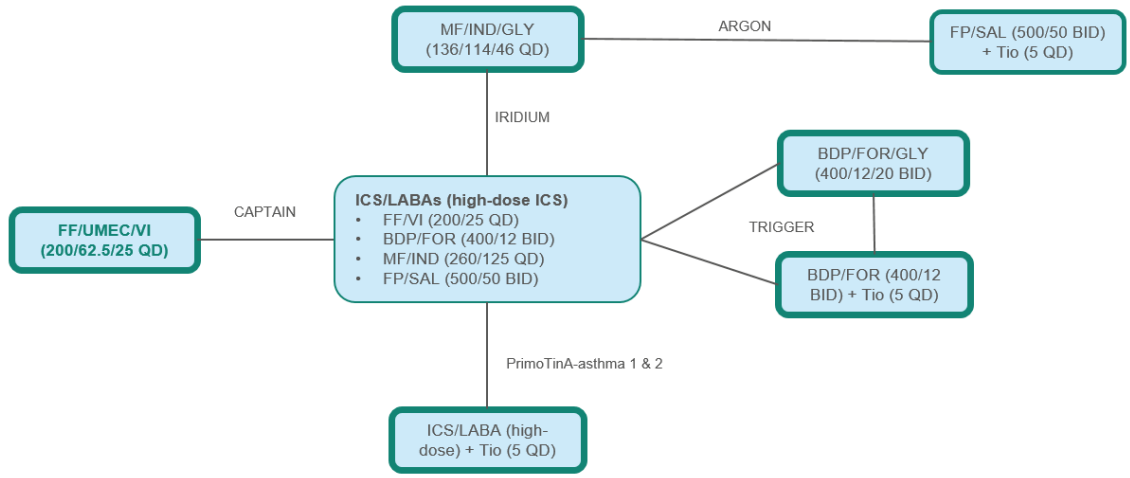
6.5 The CAPTAIN trial included evidence for two strengths of FF/UMEC/VI (100/62.5/25 and 200/62.5/25), but the submission only sought listing for the higher strength.

6.6 No randomised controlled trials comparing FF/UMEC/VI 200/62.5/25 with MF/IND/GLY 136/114/46 or FF/UMEC/VI 200/62.5/25 with high dose ICS/LABA+TIO were identified. As such, the submission presented the following two indirect treatment comparisons:

- FF/UMEC/VI 200/62.5/25 one actuation once daily versus MF/IND/GLY 136/114/46 one actuation once daily with ICS/LABA as the common comparator (CAPTAIN and IRIDIUM trials); and
- FF/UMEC/VI 200/62.5/25 one actuation once daily versus high dose ICS/LABA + TIO 2.5 two actuations once daily with MF/IND/GLY 136/114/46 and ICS/LABA as common comparators (CAPTAIN, ARGON, IRIDIUM, TRIGGER trials).

6.7 A network diagram of the trials included in the indirect comparisons is presented in Figure 1.

Figure 1: Network diagram of the trials included to inform the indirect comparisons of the proposed intervention (TRELEGY 200/62.5/25 D vs FF/IND/GLY 136/114/46 and high dose ICS/LABA+ TIO 2.5 2xD) via high dose ICS/LABA (6 trials)



Source: Figure 6, p49 of the submission

BDP: beclometasone dipropionate; BD: twice daily; FF: fluticasone furoate; FOR: formoterol fumarate; FP: fluticasone propionate; GLY: glycopyrronium bromide; ICS: inhaled corticosteroid; IND: indacaterol acetate; LABA: long-acting beta agonist; MF: mometasone furoate; QD: once daily; SAL: salmeterol; TIO: tiotropium; UMEC: umeclidinium; VI: vilanterol

Colour code:

Triple therapy – high-dose ICS | ICS/LABA – high-dose ICS

6.8 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
CAPTAIN	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, 2020
	Clinical Study Report: A Phase III, randomised, double blind, active controlled, parallel group study, comparing the efficacy, safety and tolerability of the fixed dose combination FF/UMEC/VI with the fixed dose dual combination of FF/VI, administered once-daily via a dry powder inhaler in subjects with inadequately controlled asthma	2019
PrimoTinA NCT00772538 and NCT00776984	Tiotropium in asthma poorly controlled with standard combination therapy	The New England Journal of Medicine, 2012
	Tiotropium improves lung function, exacerbation rate, and asthma control, independent of baseline characteristics including age, degree of airway obstruction, and allergic status.	Respiratory Medicine, 2016
IRIDIUM NCT02571777	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
ARGON NCT03158311	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).	Respiratory Medicine, 2020
TRIGGER NCT02676089	Single inhaler extrafine triple therapy in uncontrolled asthma (TRIMARAN and TRIGGER): two double-blind, parallel-group, randomised, controlled phase 3 trials.	Lancet, 2019

Source: Table 14, pp44-46 of the submission
CSR: FF: fluticasone fumarate; FP: Fluticasone propionate; UMEC: umeclidinium; VI: vilanterol

6.9 The key features of the randomised trials are summarised in Table 3. Only the CAPTAIN and PrimoTinA1&2 trials included Australian sites.

Table 3: Key features of the included evidence for indirect comparison

Trial	N	Design/ duration	Bias	Treatment arms	Population	Key efficacy outcomes
CAPTAIN	2,436	MC, R, DB, parallel, 3w run-in + 24w tx (+7d follow-up)	Low	Triple therapies: **FF/UMEC/VI** (100/31.25/25 D; 100/62.5/25 D; 200/31.25/25 D; **200/62.5/25 D**) Double therapies: FF/VI (100/25 D; 200/25 D)	Aged ≥18y, Asthma, FEV1 ≥30% and <85%	1º: Trough FEV1 (24w) 2 º: Annualised rate of moderate/severe asthma exacerbations (24w, 52w), ACQ-7 (24w), AQLQ (24w), SGRQ (24w)
PrimoTinA 1&2	PrimoTinA-1: 459 PrimoTinA-2: 453	MC, R, DB, parallel, 4w run-in + 48w tx	Low	Triple therapies: **ICS/LABA (medium-high dose) + TIO (5 D)** Double therapies: ICS/LABA (medium-high dose)	Aged 18-75y, Asthma, FEV1 <80%	Co-1º: Peak FEV1 response (24w), Trough FEV1 (24w), Time to the first severe asthma exacerbation (48w) 2 º: peak and trough FEV1 (48w), FVC at each treatment visit, time to the first asthma exacerbation (24w), EQ5D, ACQ-7 and AQLQ (24w)
TRIGGER	1,437	MC, R, OL*, parallel, 4w run-in + 52w tx	High	Triple therapies: **BDP/FOR/GLY (400/12/20** BD) **BDP/FOR (400/12 BD) + TIO (5 D)** Double therapies: BDP/FOR (400/12 BD)	Aged ≥18y-75y, Asthma, FEV1 <80%	Co-1º: Morning pre-dose FEV1 at (26w) and the rate of moderate and severe exacerbations (52w). 2 º: Peak FEV1 change from baseline (26w), Average morning PEF change from baseline (26w), annualised rate of severe, moderate, and moderate and severe exacerbations Others: ACQ-7, PEF, rescue medication, asthma symptom-free days, asthma control days
IRIDIUM	3,092	MC, R, DB, parallel, 2w run-in + 52w tx (+30d follow-up)	Low	Triple therapy: **MF/IND/GLY 136/114/46 D** Double therapies **MF/IND DPI (160/150 and 320/150 D)** FP/SAL (500/50 BD)	Aged 18-75y, Asthma, FEV1 <80%	1º: Trough FEV1 (26w) 2º: ACQ-7 (26w) Other: spirometry^^, ACQ-7, AQLQ, SGRQ, salbutamol, exacerbations
ARGON	1,426	MC, R, OL^, parallel, 2w run-in + 24w tx (+7d follow-up)	High	**MF/IND/GLY** DPI (80/150/50** and 160/150/50** D) **FP/SAL (500/50 BD) + TIO (2.5 *2D)**	Aged ≥18y, Asthma, FEV1 <85%	1º: AQLQ (24w) 2º: Trough FEV1 and ACQ-7 (24w) Other: Spirometry^^, ACQ-7, AQLQ-S, Work Productivity and Activity Impairment Questionnaire (WPAI-Asthma), EQ-5D-5L, salbutamol, exacerbations

Source: Compiled during the evaluation based on Table 15, p48, Table 16, pp52-57, Table 22, p75-78, Table 23, p80-85 of the submission
Some information in the table was extracted from CAPTAIN CSR, Kerstjens et al. 2012 (PrimoTinA1&2), Kerstjens et al. 2020 (IRIDIUM), and Virchow et al 2019 (TRIGGER) and Gessner et al. (2020).
ACQ-7: asthma control questionnaire; AQLQ=asthma quality of life questionnaire; BDP: Beclomethasone dipropionate; B: double blind; DP: Dry Powder Inhaler; EQ-5D-5L : European Quality of life- five dimensions- five levels; FEV_{25-75}: forced expiratory flow between 25% and 75%; FF: fluticasone furoate; FP: fluticasone propionate; FOR: formoterol; FVC: forced vital capacity; GLY: glycopyrronium bromide; IND: indacaterol; MC: multicentre; MF: mometasone furoate; OL: open label; PEF: peak expiratory flow rate; R: randomised; SAL: salmeterol; TIO: tiotropium; BD: twice daily; D: Once daily; d: day; tx: treatment; UMEC: umeclidinium; w: week; VI: vilanterol; y: year

* BDP/FOR+TIO arm in the TRIGGER trial was open-label. Therefore, the evaluation assessed the risk of bias to be high. However, any bias is more likely to affect subjective outcomes, such as AQLQ score, rather than objective outcome, such as FEV1.
**The update labelled doses for 80/150/50 and 160/150/50 are 68/114/46 and 136/114/46, respectively.
^ Partial blind/open-label study. Investigators and patients had knowledge of treatment allocation between MF/IND/GLY and/or comparator, however MF/IND/GLY dosage strength allocation was masked. SAL/FP + TIO was open-label and both investigators and patients had full knowledge of treatment allocation. The global sponsor team responsible for data review and analysis was blinded to all treatment allocation.
^ ^FEV1, PEF, FVC, FEF25-75%, trough FEV1 (other visits). The PBAC previously noted that "the primary outcome, the Asthma Quality of Life Questionnaire (AQLQ), was subjective and at a high risk of bias due to the partial open label nature of the trial. As such, the PBAC considered the AQLQ results of ARGON trial were not a reliable measure to inform the clinical claim" (paragraph 7.4, MF/IND/GLY PSD, July 2020 PBAC Meeting).
Text in bold represents the intervention or one of the two comparators in the current submission

6.10 All trials were multicentre, randomised controlled trials. The mean duration of asthma at baseline ranged from 16.8 to 26.2 years in the CAPTAIN, IRIDIUM, ARGON and TRIGGER trials. The PrimoTinA-asthma 1 & 2 trial reported median rather than mean duration (26-31 years). The intended duration of treatment was 24 weeks in the ARGON trial, 48 weeks in PrimoTinA1&2 trial and 52 weeks in the CAPTAIN, TRIGGER and IRIDIUM trials.

6.11 Overall, the risk of bias in CAPTAIN, PrimoTinA1&2, and IRIDIUM was considered low; however, the risk of bias in ARGON and TRIGGER was considered high as follows:

- In the ARGON trial, patients and investigators were not blinded to treatment allocation in the fluticasone propionate (FP) /salmeterol (SAL) + TIO arm, and the primary outcome measure was a subjective measure (asthma quality of life questionnaire (AQLQ), a patient-reported questionnaire).
- The ARGON trial enrolled symptomatic patients after a run-in period with FP/SAL, therefore could result in selection bias against FP/SAL+TIO during the treatment phase. The trial also allowed patients with symptom control in the FP/SAL+TIO arm to "step down" treatment including stopping intake of TIO. This was not possible in the triple therapy arm (MF/IND/GLY), thus potentially favouring MF/IND/GLY. It follows that this would favour FF/UMEC/VI 200/62.5/25 versus multiple inhaler triple therapy in the current submission.
- In the TRIGGER trial, one of the arms (BDP/FOR+TIO) was open-label. The submission claimed that the risk of bias in TRIGGER was low. However, it was judged to be high as part of this evaluation.
- Any bias is more likely to affect subjective outcomes, such as AQLQ score, rather than objective outcome, such as FEV1.

6.12 There were differences across the trials that may violate the assumption of transitivity/exchangeability of the common reference arm and bias results of the indirect comparisons:

- The ARGON trial recruited patients who had an established history of asthma for over 6 months, while the CAPTAIN, TRIGGER and IRIDIUM trials included patients with asthma history of over 1 year. The PrimoTinA 1&2 trial required patients to have asthma history ≥5 years.

- The CAPTAIN trial included patients (approximately 15%, 364/2,426) who had no history of exacerbations in the past 12 months. This differed from the other included trials, which specified for inclusion that participants had to have experienced ≥1 exacerbations requiring systemic glucocorticoids, an emergency department visit or hospitalisation in the previous year. The requested PBS listing (clinical criteria) for FF/UMEC/VI 200/62.5/25 requires that patients have experienced at least one severe exacerbation in the previous 12 months. In this regard, the submission presented a posthoc subgroup analysis of the population in the CAPTAIN trial with ≥1 exacerbations in the previous year. The ESC noted that a high proportion of patients in the CAPTAIN trial had no history of severe exacerbations in the past 12 months (approximately 33% of the FF/VI 200/25 and FF/UMEC/VI 200/62.5/25 arms 271/814).
- Only the PrimoTinA 1 & 2 trials included forced vital capacity ≤70% as one of the inclusion criteria.
- Patients with smoking history of >20 pack-years were excluded in the ARGON trial. This differed from the other trials, which excluded current smokers or past smokers with >10 pack-years.
- The proportion of male patients ranged from 27.3% to 61%.
- The proportion of patients who were current or ex-smokers ranged from 3.6% to 31.8%.
- Differences in the ICS/LABA combinations, dosages and dose frequencies.

6.13 The primary outcome for the CAPTAIN trial was change from baseline in trough forced expiratory volume in one second (FEV1). The submission reported the following secondary outcomes of interest: annualised rate of moderate/severe exacerbations, time to first moderate/severe exacerbation, ACQ-7 total score, ACQ-7 responder rate, AQLQ total score, and St George's Respiratory Questionnaire (SGRQ).

6.14 The clinically relevant outcomes for asthma are differences in lung function tests, rescue medication use, symptom-free days/control (e.g., Asthma Control Questionnaire, ACQ), asthma exacerbations and quality of life (e.g., AQLQ). In past decisions, the PBAC has relied on lung function tests to determine non-inferiority between ICS/LABA FDCs, including change in morning peak expiratory flow (PEF), and less commonly change in trough FEV1. The PBAC recommended TIO for triple therapy ICS/LABA+LAMA in severe asthma based on acceptable cost-effectiveness versus dual therapy ICS/LABA, supported by a clinically relevant improvement in FEV1 in the trial data and where ACQ-7 and exacerbations informed the health states in the model (paragraph 6.9, tiotropium bromide PSD, March 2016 PBAC meeting). The recommendation of MF/IND/GLY was based on improvement in trough FEV1 (paragraph 7.5, MF/IND/GLY PSD, July 2020 PBAC Meeting).

6.15 The submission nominated a non-inferiority margin of 0.10 L in the mean change from baseline in clinic trough FEV1 at the end of the treatment period. The PBAC previously

considered that an increase in FEV1 of 0.10 L was likely to be clinically meaningful for severe asthma (paragraph 7.5, tiotropium bromide PSD July 2015 PBAC meeting), which is lower than the non-inferiority margin of between 0.15 to 0.20 L accepted by the PBAC for less severe asthma (page 4, fluticasone propionate with eformoterol fumarate FDC PSD, July 2013 PBAC Meeting; and paragraph 6.4, fluticasone furoate with vilanterol FDC PSD, March 2014 PBAC Meeting). A non-inferiority margin of 0.10 L for severe asthma is consistent with the sample size calculations for the CAPTAIN and PrimoTinA1&2 trials but not for the IRIDIUM and TRIGGER trials (0.09 L).

6.16 The submission did not specify a non-inferiority margin for the other outcomes and instead considered the lack of a statistical difference between FF/UMEC/VI 200/62.5/25 and comparators as supporting the claim of non-inferiority. The ESC considered it reasonable, based on prior PBAC decisions, to rely predominantly on the primary outcome (FEV1) for the purposes of assessing non-inferiority whilst noting that non-inferiority was not established for the secondary outcome measures including rates of moderate/severe exacerbations. The ESC also noted that no precedents were found for non-inferiority margins for the time to first moderate/severe exacerbation or ACQ-7 responder rates.

Comparative effectiveness

6.17 Tables 4-6 provide the CAPTAIN trial results for primary and secondary outcomes. As outlined in paragraph 6.12, the CAPTAIN trial differed from the other trials with respect to exacerbation history. Where possible, the results for both the ITT and the subgroup analysis of patients with ≥1 exacerbation are presented.

6.18 The CAPTAIN trial also included the medium strength FF/UMEC/VI with the results for FF/UMEC/VI 100/62.5/25 presented in the submission but not reproduced here.

Table 4: Change from baseline in trough FEV1 and % of patients having >100 mL improvement (i.e. responder) from baseline for trough FEV1 (ITT and subgroup results based on the CAPTAIN trial)

	ITT population		Subgroup ≥1 exacerbation	
	FF/VI 200/25 N=406	**FF/UMEC/VI 200/62.5/25 N=408**	**FF/VI 200/25 N=248**	**FF/UMEC/VI 200/62.5/25 N=283**
Mean change from baseline trough FEV1 at Week 24				
Mean change (SE), 95% CI (L)	0.076 (0.0156) (0.045, 0.106)	0.168 (0.0155) (0.137, 0.198)	0.076 (0.0198) (0.037, 0.114)	0.153 (0.0186) (0.117, 0.190)
FF/UMEC/VI 200/62.5/25 vs FF/VI 200/25 (L) Difference (SE), 95% CI, p-value	Reference arm	**0.092 L (0.0220 L) (0.049 L, 0.135 L) p<0.001**	Reference arm	**0.078 L (0.0272 L) (0.024 L, 0.131 L), p<0.0042^**
% of patients having >100 mL improvement (i.e. responder) from baseline for trough FEV1 at week 24 and 52				
Week 24			NR	
n Responder Non-responder Non-responder due to missing data	406 151 (37%) 255 (63%) 21 (5%)	408 210 (51%) 198 (49%) 17 (4%)		
FF/UMEC/VI 200/62.5/25 vs. FF/VI 200/25 Odds Ratio (95% CI); p-value	Reference arm	**1.82 (1.37, 2.41); <0.001**		
Week 52				
n Responder Non-responder Non-responder due to missing data	101 37 (37%) 64 (63%) 12 (12%)	100 52 (52%) 48 (48%) 9 (9%)		
FF/UMEC/VI 200/62.5/25 vs. FF/VI 200/25 Odds Ratio (95% CI); p-value	Reference arm	**1.91 (1.07, 3.40); 0.028**		

Source: Tables 26-27, pp93-94, Table 44, p108 of the submission

CI: confidence interval; FF: fluticasone furoate; N: total participants in group; NR: Not reported; UMEC: umeclidinium; VI: vilanterol

Note: A responder is defined as an improvement (increase) in trough FEV1 ≥100 mL from baseline.

A non-responder was defined as having a decrease, no change or an increase from baseline of <100 mL, or missing trough FEV1 at the post-baseline visit. If trough FEV1 was missing at baseline, responder status is missing and subjects are excluded from the analysis.

Analysis performed using a generalised linear mixed model with a logit link function and covariates of treatment, age, sex, region, visit, pre-study ICS dose at screening, baseline visit, baseline value by visit and treatment by visit interactions.

^Calculated using the following formula: exp (−0.717*z − 0.416*z^2), where z= mean difference/SE, SE= (upper limit- lower limit)/(2*1.96)

Bold indicates statistically significant results based on a priori analysis

6.19 Numerically, the ITT population observed greater incremental change from baseline in trough FEV1 in the FF/UMEC/VI 200/62.5/25 group versus the FF/VI 200/25 (0.092 L) compared to the subgroup having ≥1 exacerbation (0.078 L) (see Table 4). Both results were statistically significant (p<0.05). In the July 2020 MF/IND/GLY submission, the ESC considered that the lung function improvements [i.e., the mean difference in trough FEV1 of 0.073 L (95% CI 0.03, 0.12) [3]] for MF/IND/GLY were comparable with those demonstrated in other studies evaluating the benefit of LAMA in addition to LABA/ICS in similar patient populations (paragraph 6.16, MF/IND/GLY

[3] Virchow JC et al. Single inhaler extra fine triple therapy in uncontrolled asthma (TRIMARAN and TRIGGER): two double-blind, parallel group, randomised, controlled phase 3 trials. Lancet 2019;394:1737-49.

PSD, July 2020 PBAC Meeting). The PSCR noted that the mean difference in trough FEV1 of 0.073 L reported for MF/IND/GLY in July 2020 was numerically lower than the 0.078 L benefit demonstrated for FF/UMEC/VI versus dual therapy in the CAPTAIN trial.

6.20 In the CAPTAIN ITT population, the proportion of patients with >100mL improvement from baseline for trough FEV1 was higher for the FF/UMEC/VI 200/62.5/25 group compared with FF/VI 200/25 group (at both week 24 and 52). The results were statistically significant (p<0.05). These results are similar to those reported in July 2020 where MF/IND/GLY arms had a higher proportion of responders compared with dual therapies (MF/IND and FP/SAL) (paragraph 6.16, MF/IND/GLY PSD, July 2020 PBAC Meeting).

Table 5: Asthma exacerbation outcomes (ITT and subgroup results based on the CAPTAIN trial)

	ITT population		Subgroup ≥1 exacerbation	
	FF/VI 200/25 N=406	**FF/UMEC/VI 200/62.5/25 N=408**	**FF/VI 200/25 N=249**	**FF/UMEC/VI 200/62.5/25 N=284**
Annualised rate of moderate/severe asthma exacerbations across weeks 1 to 52				
Mean annualised rate (95% CI)	0.57 (0.47, 0.69)	0.55 (0.45, 0.67)	0.72 (0.57, 0.91)	0.58 (0.46, 0.74)
Rate ratio (95% CI) p-value % reduction (95% CI)	Reference arm	0.97 (0.73, 1.28) p=0.818 3.2 (-28.2, 27.0)	Reference arm	0.80 (0.58, 1.12) 19.6 (-11.9, 42.3)
Time to first moderate/severe asthma exacerbation				
Probability of having event (%) (95% CI)	37.0 (30.1, 45.0)	40.7 (33.7, 48.6)	44.4 (35.2, 54.9)	39.3 (31.5, 48.1)
Hazard Ratio (95%CI)	Reference arm	1.04 (0.79, 1.36)	Reference arm	0.94 (0.69, 1.28)
Percentage reduction in risk (%) (95% CI); p-value	Reference arm	-3.8 (-35.8, 20.6) 0.784	Reference arm	6.3 (-28.0, 31.4)
Annualised rate of severe asthma exacerbations across weeks 1 to 52				
Mean annualised rate (95% CI)	0.26 (0.20, 0.34)	0.23 (0.17, 0.30)	NR	
Rate ratio (95% CI); p-value	Reference arm	0.88 (0.60, 1.31); p=0.540		
% reduction (95% CI)	Reference arm	11.60% (-31.10%, 40.40%)		
Time to first severe asthma exacerbations				
Probability of having event (95% CI)	20.80 (15.3, 27.9)	33.8 (15.6, 63.2)		
Hazard ratio (95% CI)	Reference arm	0.93 (0.64, 1.34)		
% reduction in risk (95% CI); p value	reference arm	7.2 (-34.1, 35.8); p=0.692		

Source: Tables 28-31, p94-96, Table 45, p109, Table 46, p110 of the submission
CI: Confidence Interval; FF: Fluticasone Furoate; UMEC: Umeclidinium; VI: Vilanterol; NA: Not applicable

6.21 A trend for greater reductions in moderate or severe exacerbations was reported for the comparison of the FF/UMEC/VI 200/62.5/25 group versus the FF/VI 200/25 group in the subgroup with ≥1 exacerbation in the past 12 months than in the ITT population

(rate ratio 0.80 and 0.97, respectively) (see Table 5). However, there was no statistically significant difference between FF/UMEC/VI 200/62.5/25 and FF/VI 200/25 in terms of all endpoints related to exacerbations. The submission did not present a subgroup analysis of the annualised rate of severe asthma exacerbations as the severe exacerbation rate was low in the study (p109 of the submission). This would result in substantial variability in the estimated effects.

6.22 Similar trends to improvement in ACQ7 change from baseline were observed for the subgroup of patients with ≥1 exacerbation in the past 12 months compared with the ITT population (change from baseline: -0.062 and -0.059 for the ITT and the subgroup, respectively) (see Table 6).

Table 6: Mean change from baseline in ACQ-7 total score and proportion of responders (MCID ≥0.5 points) at week 24 (ITT and subgroup results based on the CAPTAIN trial)

	ITT population		Subgroup ≥1 exacerbation	
	FF/VI 200/25 N=406	**FF/UMEC/VI 200/62.5/25 N=408**	**FF/VI 200/25 N=241**	**FF/UMEC/VI 200/62.5/25 N=274**
Mean change from baseline in ACQ-7 total score at week 24				
Mean change (SE), 95% CI	-0.717 (0.0339) (-0.784, -0.651)	-0.779 (0.0339) (-0.846, -0.713)	-0.662 (0.0430) (-0.746, -0.578)	-0.721 (0.0405) (-0.801, -0.642)
FF/UMEC/VI 200/62.5/25 vs FF/VI 200/25 Difference (SE), 95% CI	Reference arm	-0.062 (0.0479) (-0.156, 0.032)	Reference arm	-0.059 (0.0590) (-0.175, 0.056)
Percent of responders according to ACQ-7 total score from baseline at week 24				
 Responder Non-responder Non-responder due to missing data	N=397 231 (58%) 166 (42%) 23 (6%)	N=395 251 (64%) 144 (36%) 19 (5%)	N=243 141 (58%) 102 (42%) 9 (4%)	N=275 164 (60%) 111 (40%) 15 (5%)
Odds ratio (95% CI), p-value	Reference arm	1.28 (0.95, 1.72); p= 0.102	Reference arm	1.08 (0.75, 1.56); p= 0.693

Source: Tables 34,37, pp99-101, Table 48, p112 of the submission
ACQ-7: Asthma control Questionnaire; CI: Confidence Interval; FF: Fluticasone Furoate; UMEC: Umeclidinium; VI: Vilanterol
^Difference of mean change in ACQ-7 total score at week 24
^^Calculated using an online calculator (https://www.medcalc.org/calc/comparison_of_proportions.php). Results are based on a Chi-square test.

6.23 Similar improvements in AQLQ change from baseline were observed for patients with ≥1 exacerbation in the past 12 months compared with the ITT population (change from baseline: -0.01 and 0.04 for the ITT and the subgroup, respectively) (not statistically significant). The submission also presented St George's Respiratory Questionnaire (SGRQ) change from baseline to provide additional support for the other patient-related outcome results for FF/UMEC/VI 200/62.5/25. There was no statistically significant difference between FF/UMEC/VI 200/62.5/25 and FF/VI 200/25 in terms of SGRQ total score.

6.24 The evaluation considered FF/UMEC/VI 200/62.5/25 was superior to FF/VI 200/25 for the outcomes based on trough FEV1 for both the ITT population and the ≥1 prior exacerbation subgroup.

6.25 The submission presented two indirect treatment comparisons comparing FF/UMEC/VI 200/62.5/25 with MF/IND/GLY 136/114/46 or FF/UMEC/VI 200/62.5/25 with high dose ICS/LABA+TIO. The following endpoints were included in the indirect treatment comparisons:

- Trough FEV1 at week 24
- Annualised rate of moderate/severe exacerbation at week 52
- Time to first moderate/severe exacerbation
- ACQ7 score change from baseline at week 24
- ACQ7 responder at week 24.

6.26 The submission reported that the trial populations were matched for comparison where possible. The CAPTAIN population subgroup with ≥1 severe exacerbation in the past 12 months was used for the comparison as this aligns with the requested restriction. The CAPTAIN ITT was also included in the comparison. As outcomes differed between trials, the indirect treatment comparison was conducted for matching trial outcomes with the CAPTAIN trial. Table 7 presents the indirect treatment comparison results.

Table 7: Summary effectiveness results based on indirect comparison

	Interpretation	FF/UMEC/VI 200/62.5/25 vs MF/IND/GLY 136/114/46 mean (95% CI); p value		FF/UMEC/VI 200/62.5/25 vs high dose ICS/LABA+TIO mean (95% CI; p value)	
		CAPTAIN ITT	CAPTAIN ≥1 exacerbation	CAPTAIN ITT	CAPTAIN ≥1 exacerbation
Trough FEV1, 24 weeks (mL)	High numbers better	0.55 (-52.26, 53.36); p=0.98	-13.45 (-74.87, 47.97); p=0.67	35.67 (-91.01,162.35); p=0.58	21.67 (-108.83,152.17); p=0.74
Annualised rate moderate/severe exacerbation, 52 weeks (rate ratio)	High numbers worse	1.33 (0.82, 2.16); p=0.25	1.10 (0.65, 1.84); p=0.73	1.18 (0.84, 1.66); p=0.34	0.97 (0.66, 1.44); p=0.89
Time to first moderate/severe exacerbation (hazard ratio)	High numbers worse	1.35 (1.00, 1.82); p=0.05	1.22 (0.87, 1.71); p=0.24	1.26 (0.88, 1.80); p=0.20	1.14 (0.77, 1.68); p=0.51
Change from baseline in ACQ-7 Total Score: 24 weeks (exl. PrimoTINA)	High numbers worse	-0.026 (-0.121, 0.069); p=0.59	-0.023 (-0.139, 0.093); p=0.70	-0.059 (-0.260, 0.142); p=0.56	-0.056 (-0.268, 0.156); p=0.60
ACQ-7 responder rate (odds ratio)	High numbers better	1.18 (0.81, 1.71), p=0.38	1.00 (0.65, 1.53); p=0.98	1.10 (0.72, 1.69); p=0.66	0.93 (0.58, 1.50); p=0.76

Source: Table 56, p128, Table 59, p134, Table 60, p135, Table 62, p138, Table 63, p139 Table 67, p143, Table 68, p144, Table 72, p149, Table 73, p151 of the submission.
ACQ-7=Asthma Control Questionnaire; FEV1=forced expiratory volume in one second; PSD = Public Summary Document; SE = Standard error.

6.27 The submission reported that for the CAPTAIN study primary outcome, trough FEV1 at week 24, when compared to both MF/IND/GLY 136/114/46 and high-dose ICS/LABA + TIO 2.5, FF/UMEC/VI 200/62.5/25 demonstrated non-inferiority with both the CAPTAIN ITT population and the CAPTAIN subgroup with ≥1 severe exacerbation in the past 12 months based on the specified non-inferiority margin (0.10 L). For all other outcomes included in the indirect treatment comparison, no significant difference was found with FF/UMEC/VI 200/62.5/25 compared to both MF/IND/GLY 136/114/46 and high-dose ICS/LABA + TIO 2.5.

6.28 Given a non-inferiority margin of 0.10 L, FF/UMEC/VI 200/62.5/25 was not non-inferior compared to high dose ICS/LABA+TIO (multiple inhaler triple therapy) for trough FEV1 in the subgroup meeting the PBS restriction (≥1 exacerbation in previous 12 months) as the lower 95% CI (-0.11 L) exceeded -0.10 L. FF/UMEC/VI 200/62.5/25 was non-inferior compared to MF/IND/GLY 136/114/46 for trough FEV1 for the ITT group and for the subgroup meeting the PBS restriction.

Comparative harms

6.29 The submission did not conduct a formal indirect comparison of adverse events to assess the non-inferiority of FF/UMEC/VI 200/62.5/25 compared to MF/IND/GLY 136/114/46 or ICS/LABAs + LAMA.

6.30 The incidence rate of 'any adverse events' was higher for FF/UMEC/VI 200/62.5/25 in the CAPTAIN trial compared with MF/IND/GLY 136/114/46 in the IRIDIUM trial. However, serious and treatment-related adverse events were similar for both treatments.

6.31 Table 8 presents the safety outcomes across the remaining included trials.

Table 8: Comparison of clinical adverse events (number of patients (%))

Study	Any adverse event	Serious AEs	Treatment-related AEs	Treatment-related serious AEs
ARGON				
IND/GLY/MF (150/50/160 µg) D	52%	4%	6%	0%
SAL/FP (50/500 mcg) BD + TIO 5µg D	52%	4%	4%	0%
CAPTAIN				
FF/UMEC/VI 200/31.25/25 mcg	48%	6%	5%	0%
FF/UMEC/VI 200/62.5/25 mcg	53%	5%	5%	0%
FF/VI 200/25 mcg	52%	5%	4%	0%
PrimoTinA1				
ICS/LABA (high dose) + PBO	77%	7%	-	-
ICS/LABA (high dose) + TIO (5 µg) D	71%	8%	-	-
PrimoTinA2				
ICS/LABA (high dose) + PBO	84%	11%	-	-
ICS/LABA (high dose) + TIO (5 µg) D	77%	9%	-	-
TRIGGER				
BDP/FOR (200/6 µg) 2 inhalations BD	77%	16%	4%	0%
BDP/FOR (200/6 µg) 2 inhalations BD + TIO (2.5 µg) 2 inhalations D	73%	10%	6%	0%
BDP/FOR/GLY (200/6/10 µg) 2 inhalations BD	72%	11%	5%	0%

Source: Table 75, p154 of the submission

AE: Adverse events; BDP: beclometasone dipropionate; BD: twice daily; FF: fluticasone furoate; FOR: formoterol fumarate; FP: fluticasone propionate; GLY: glycopyrronium bromide; ICS: inhaled corticosteroid; IND: indacaterol acetate; LABA: long-acting beta agonist; MF: mometasone furoate; D: once daily; SAL: salmeterol; TIO: tiotropium; UMEC: umeclidinium; VI: vilanterol

6.32 The most frequently reported AEs across the treatment arms of the CAPTAIN trial were nasopharyngitis (range: 13% to 15%), headache (5% to 9%), upper respiratory tract infection (3% to 5%), and bronchitis (3% to 5%).

Clinical claim

6.33 The submission described the efficacy of FF/UMEC/VI 200/62.5/25 mcg as non-inferior to MF/IND/GLY 136/114/46 mcg in the treatment of patients with asthma who remain uncontrolled on ICS/LABA. Further, it described FF/UMEC/VI 200/62.5/25 mcg to be non-inferior to high dose ICS/LABA + TIO in the treatment of patients with asthma who remain uncontrolled on ICS/LABA.

6.34 The evaluation considered the clinical claim of non-inferior efficacy was uncertain due to the following reasons:

- No head-to-head trials comparing FF/UMEC/VI 200/62.5/25 to MF/IND/GLY 136/114/46 or high dose ICS/LABA + TIO were presented.
- The ARGON and TRIGGER trials have a high risk of bias since the SAL/FP+TIO arm in the ARGON trial and BDP/FOR+TIO in the TRIGGER trial were open-label. Any bias is more likely to affect subjective outcomes, such as AQLQ score, rather than objective outcomes, such as FEV1.
- There were differences across the trials that may violate the assumption of transitivity/exchangeability of the common reference arm and bias results of the

indirect comparisons (gender, the proportion ex-smokers, previous exacerbations, and ICS/LABA and ICS/LABA+LAMA combinations, dosages and dose frequencies).

6.35 The evaluators considered that it may be reasonable to conclude non-inferiority of FF/UMEC/VI 200/62.5/25 versus MF/IND/GLY 136/114/46 and versus high dose ICS/LABAs + TIO if change in trough FEV1 is considered to be the most relevant outcome. The PSCR argued the PBAC recently considered MF/IND/GLY non-inferior utilising a clinical claim based on trough FEV1. The ESC agreed with the PSCR and considered a claim of non-inferior efficacy was supported by the FEV1 evidence presented in the submission.

6.36 The submission claimed that FF/UMEC/VI 200/62.5/25 was non-inferior in terms of safety compared to MF/IND/GLY 136/114/46 and high dose ICS/LABAs + TIO. Given that treatment related adverse event rates were similar across treatments in each trial, the ESC considered it was reasonable to suggest that the safety of FF/UMEC/VI 200/62.5/25 appeared similar to that of high dose MF/IND/GLY 136/114/46 and high dose ICS/LABAs + TIO.

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

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

Economic analysis

6.39 The submission presented a cost-minimisation analysis comparing FF/UMEC/VI 200/62.5/25 and MF/IND/GLY 136/114/46, the main comparator, and versus high dose ICS/LABA + TIO. The analysis assumed no additional costs or cost-offsets. The PBAC considered this was appropriate.

6.40 The submission proposed the following equi-effective doses based on the trial evidence presented:

- FF/UMEC/VI 200/62.5/25 one actuation daily = MF/IND/GLY 136/114/46 one actuation daily.

The dose relativities for FF/UMEC/VI 200/62.5/25 one actuation daily versus high dose ICS/LABA + TIO are provided in Table 9.

Table 9: Equi-potent high dose ICS/LABA FDCs and LAMA and high dose ICS/LABA/LAMA FDCs listed on the PBS for asthma

		"High" dose ICS/LBA FDCs, providing >800mcg budesonide equi-potent per day for 30 days
Multiple inhaler triple therapy	DPI ICS/ LABA	FP/SAL 500/50mcg BD (Seretide® Accuhaler®, 60 actuations) BUD/FOR 400/12mcg 2 BD (Symbicort® Turbuhaler®, Duoresp® Spiromax®, 120 actuations) FF/VI 200/25mcg D (Breo® Ellipta®, 30 actuations)
	DPI caps ICS/ LABA	MF/IND 320/150mcg D (Atectura® Breezhaler®, 30 actuations)
	MDI ICS/LABA	FP/SAL 250/25mcg 2 BD (Seretide®, Evocair®, Fluticasone + Salmeterol Cipla®, Pavtide®, SalPlusF Inhaler®, Seroflo®, 120 actuations) BUD/FOR 200/6mcg 4 BD (Symbicort® Rapihaler®, 2x120 actuations) FP/FOR 250/10mcg 2 BD (Flutiform®, 120 actuations)
	PLUS LAMA	Tiotropium 2.5mcg 2 D (Spiriva®, 60 actuations)
Single inhaler triple therapy	DPI capsules ICS/ LABA/ LAMA	MF/IND/GLY 136/114/46mcg D (Enerzair® Breezhaler®, 30 actuations)

Source: Table 84, pp163-164 of the submission
BEC=beclometasone; BUD=budesonide; DPI=dry powder inhaler; FOR=formoterol; FF=fluticasone furoate; FP=fluticasone propionate; IND=indacaterol; MDI=metered dose inhaler; MF=mometasone furoate; SAL=salmeterol; VI=vilanterol; D=once daily; BD=twice daily
Note: The equi-potent doses shown in the table are based on Table 8, P19 of MF/IND/GLY PSD, July 2020 PBAC Meeting. The submission also updated the table to include Atectura (medium or high dose MF/IND)
Tiotropium is the only PBS-listed LAMA to treat asthma.

6.41 Based on the cost-minimisation analysis presented in the submission the requested price for FF/UMEC/VI 200/62.5/25 was the same as for MF/IND/GLY 136/114/46 (AEMP = $74.01). The submission also noted that the AEMP requested for FF/UMEC/VI 200/62.5/25, is also equivalent to the least costly multiple inhaler triple therapy consisting of a high dose ICS/LABA (AEMP $45.19) + LAMA (AEMP $28.82) available on the PBS.

Drug cost/patient/year

6.42 The annual cost of FF/UMEC/VI 200/62.5/25 was $1,115.23. This calculation assumes 12.175 scripts per year at the requested DPMQ ($91.60).

Estimated PBS usage & financial implications

6.43 This submission was not considered by DUSC. The submission adopted a market share approach to forecast the cost of FF/UMEC/VI 200/62.5/25 as an alternative to high dose ICS/LABAs + LAMA products listed on the PBS for asthma. This approach was adopted as there are only limited utilisation data for MF/IND/GLY 136/114/46, which was PBS-listed on 1 April 2021.

6.44 Table 10 summarises the key inputs used in the financial estimates.

Table 10: Summary of data sources for estimating utilisation

Data	Value	Description	Data sources	Comment
Total scripts and estimated annual rate of growth	Year 0 (2021): 358,424 % increase in year 1: 8% % increase from year 2 - year 6: 5%	Based on TIO prescription data from the year 2020. Assumed each tiotropium prescription = one medium or high dose ICS/LABA.	Medicare Statistics, 2021 Growth rates based on MF/IND/GLY PSD July 2020	Item 11043F is restricted to triple therapy in combination with ICS/LABA. Similar growth rates were assumed for MF/IND/GLY.
Market share	Market share of: - seven high dose ICS/LABAs: 70.21% - Medium-dose ICS/LABAs: 29.79%	Market share of seven different high dose ICS/LABAs (of interest for calculations). The rate of 70.21% was applied for all years^.	Prospection data, a 10% longitudinal patient sample of PBS reimbursed prescriptions	The evaluation considered this was reasonable.
Total single inhaler triple therapy market share in triple therapy in asthma	Single inhaler triple therapy % of total triple therapy: Year 0: 10.5% Year 1: 24.84% Year 2: 32.39% Year 3: 38.58% Year 4: 43.94% Year 5: 48.57% Year 6: 52.59%	Single inhaler triple therapy uptake in total COPD triple-therapy market from year 2 of a triple being available on the PBS.	Prospection data, a 10% longitudinal patient sample of PBS reimbursed prescriptions	The PBAC previously noted that "…..there is no requirement that LAMA/LABA FDCs must be used in combination with ICS for COPD (and therefore cannot proxy for triple therapy scripts)" (Table 9, MF/IND/GLY PSD, July 2020 PBAC Meeting).
Uptake rate of FF/UMEC/VI 200/62.5/25 within single inhaler triple therapy market	Base case model: 50%: 50% split across MF/IND/GLY 136/114/46 and FF/UMEC/VI 200/62.5/25	Assumed due to the lack of any MF/IND/GLY 136/114/46 prescribing data currently. This equal market share split was carried forward for the 6 years of the model.	Assumption	The evaluation considered the uptake of FF/UMEC/VI 200/62.5/25 is likely to be comparatively higher due to the patients' and physicians' familiarity with the Ellipta device (as FF/UMEC/VI 100/62.5/25 is already PBS-listed to treat COPD). However, given the price is the same, it will not affect the overall cost of the single inhaler triple therapy market cost (p186 of the submission).
Patients drug compliance	100%	NA	Assumption	Compliance is unlikely to be 100% but the assumption is conservative. A sensitivity analysis was conducted to test this assumption.
Cost of treatment	$1,115* per year	NA	Estimated during the evaluation	NA
Patient co-payment per script	$9.97**	NA	Estimated during the evaluation	NA

Source: Table 87, pp171-172, Table 89, p174, 91, p177 and "2d. Scripts- Market" Sheet of "Attachment 14 Trelegy section 4.xlsx"
COPD: chronic obstructive pulmonary disease; FDC: fixed dose combination; ICS: inhaled corticosteroid; LABA: long acting beta agonist; N/A: Not applicable; PBS: pharmaceutical benefits scheme; PSD: public summary document

* This calculation assumes 12.175 scripts per year at the requested DPMQs ($91.60).
** Estimated as Total co-payments*DPMQ/Total costs
^ ICS/LABAs for COPD and asthma were separated during the analysis. Drugs specifically coded for COPD include: Onbrez (indacaterol), Spiriva (tiotropium (COPD codes only)), Bretaris (aclidinium), Incruse (umeclidinium), Seebri (glycopyrronium), Anoro (umeclidinium/vilanterol), Ultibro (glycopyrronium/indacaterol), Brimica (aclidinium/formoterol), Spiolto (tiotropioum/olodaterol), Trelegy Ellipta 100/62.5/25 mcg and Braltus (tiotropium (COPD codes only))

6.45 Table 11 summarises the estimated use and financial impact of the requested listing for FF/UMEC/VI 200/62.5/25.

Table 11: Estimated use and financial implications to the PBS/RPBS

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimation of use and financial impact of the proposed medicine PBS/RPBS						
FF/UMEC/VI 200/62.5/25						
Total scripts	[redacted][1]	[redacted][2]	[redacted][3]	[redacted][4]	[redacted][5]	[redacted][6]
PBS/RPBS cost	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]
PBS/RPBS co-payments	-[redacted][8]	-[redacted][8]	-[redacted][8]	-[redacted][8]	-[redacted][8]	-[redacted][8]
PBS/RPBS net cost (less co-payment)	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]
Net cost over 6 years						[redacted][9]
Estimation of changes in use and financial impact of other medicines						
ICS/LABA FDC + TIO (i.e., multiple inhaler triple therapy)						
Total scripts	-[redacted][4]	-[redacted][6]	-[redacted][7]	-[redacted][7]	-[redacted][7]	-[redacted][7]
PBS/RPBS affected medicines costs	-[redacted][8]	-[redacted][8]	-[redacted][8]	-[redacted][8]	-[redacted][8]	-[redacted][8]
PBS/RPBS multiple inhaler triple therapy (co-payment)	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]
PBS/RPBS net cost (less co-payment)	-[redacted][8]	-[redacted][8]	-[redacted][8]	-[redacted][8]	-[redacted][8]	-[redacted][8]
Net cost over 6 years						-[redacted][9]
Net financial implications						
Net total cost to PBS/RPBS	-[redacted][8]	-[redacted][8]	-[redacted][8]	-[redacted][8]	-[redacted][8]	-[redacted][8]
Net cost over 6 years						-[redacted][8]

Source: Table 92, pp 177-178, Table 93, pp179-180, Table 94, p181 of the submission
FDC: fixed dose combination; FF: fluticasone furoate; ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; PBS=pharmaceutical benefits scheme; RPBS= repatriation pharmaceutical benefits scheme; TIO: Tiotropium; UMEC: umeclidinium; VI: vilanterol
The redacted values correspond to the following ranges:
[1] 30,000 to < 40,000
[2] 40,000 to < 50,000
[3] 50,000 to < 60,000
[4] 60,000 to < 70,000
[5] 80,000 to < 90,000
[6] 90,000 to < 100,000
[7] 100,000 to < 200,000
[8] $0 to < $10 million
[9] $30 million to < $ 40 million

6.46 At the requested price (DPMQ = $91.60), the proposed listing of FF/UMEC/VI 200/62.5/25 was estimated to result in cost-savings to the PBS/RPBS of $0 to < $10 million over the first six years of listing. Cost savings were predicted because the financial model assumed a basket of multiple inhaler triple therapies would be displaced by the introduction of FF/UMEC/VI 200/62.5/25, most of which were more expensive than FF/UMEC/VI 200/62.5/25.

6.47 The submission did not test the possibility of FF/UMEC/VI 200/62.5/25 being substituted for dual therapy (ICS/LABA FDCs) in patients not indicated for FF/UMEC/VI 200/62.5/25. This possibility was explored in the MF/IND/GLY commentary and was found to have an impact on expenditure. The PSCR stated that in the MF/IND/GLY submission, a sensitivity analysis was conducted exploring the proportion of use in patients with controlled asthma on ICS/LABA (same total number of scripts) with 10% and 20% scenarios of substituting for ICS/LABA (instead of pure switching from multiple-inhaler triple therapy). The PSCR also noted the subsequent MF/IND/GLY commentary reported a threshold analysis where ≥3% use in patients controlled on dual therapy resulted in a net cost to the PBS/RPBS (all else constant), because dual therapy was less costly than triple therapy. The PSCR argued that given the prices of high dose ICS/LABAs remain the same and the proposed price of FF/UMEC/VI 200/62.5/25 in this submission is the same as that of MF/IND/GLY (136/114/46), the same threshold of 3% would apply.

6.48 The ESC noted that in July 2020, when considering the financial estimates of MF/IND/GLY, the PBAC "remained concerned about the risk of inappropriate use in patients with less severe asthma otherwise managed on ICS or ICS/LABA and considered a more restrictive Authority Required type listing than 'Streamlined' would be appropriate to minimise this risk" (paragraph 7.8, MF/IND/GLY PSD, July 2020 PBAC Meeting). The ESC considered this was also likely to be applicable in the case of FF/UMEC/VI 200/62.5/25. In addition, the ESC noted the FF/UMEC/VI 200/62.5/25 product is not PBS listed for COPD and considered there is a chance of use in patients with COPD who do not have asthma. The pre-PBAC response stated the sponsor has educated over 5,000 GPs on the use of low dose FF/UMEC/VI (100/62.5/25) in symptomatic COPD patients with exacerbation history. The pre-PBAC response noted that such education highlighted the increased pneumonia events with a higher dose of ICS with no additional benefit in COPD patients. In addition, the pre-PBAC response argued that there has been wide education from peak bodies highlighting increased events of osteoporosis/fractures with high dose of ICS and promoting the judicious use in the appropriate patients.

Quality Use of Medicines

6.49 The submission mentioned several factors, including inhalation technique, inhaler device, patient adherence and patient preference for a particular inhaler device that could influence the quality use of medicine for severe asthma patients. Other quality use of medicines concerns included medication errors and the potential for off-label use. The potential for off-label use of FF/UMEC/VI 200/62.5/25 could be high. This was raised as an issue for MF/IND/GLY in July 2020 and part of the reason the PBAC considered an Authority Required (telephone/online) listing appropriate (paragraph 7.8, MF/IND/GLY PSD, July 2020 PBAC Meeting).

6.50 Given FF/UMEC/VI 200/62.5/25 is a single inhaler, it is possible for patients who could be stabilised on dual therapy, to be escalated up the treatment algorithm quicker than

required to FF/UMEC/VI 200/62.5/25. This highlights the need for concerted patient and prescriber education. The pre-PBAC response argued the AAH provides clear guidance on when to step up after ensuring that adherence, inhaler technique and other comorbidities are carefully checked before considering any increase in dose or addition of treatment regimen. The pre-PBAC response stated that the sponsor would provide educational material (including case studies which shall be developed in consultation with respiratory specialists) which emphasized this important aspect of asthma management so that only the right patients are stepped up to FF/UMEC/VI.

Financial Management – Risk Sharing Arrangements

6.51 The pre-PBAC response proposed a risk sharing arrangement (RSA) as a mechanism to reduce the perceived risk of inappropriate prescribing to the PBS budget instead of an Authority Required (telephone/online) listing.

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

7 PBAC Outcome

7.1 The PBAC recommended the Authority Required (STREAMLINED) listing of fluticasone furoate (FF) with vilanterol (VI) and umeclidinium (UMEC) fixed dose combination (FDC) for maintenance therapy of severe asthma. The recommended listing was for one strength: FF/UMEC/VI 200/62.5/25 mcg.

7.2 The PBAC considered the claim of non-inferior effectiveness and safety to the FDC of mometasone furoate (MF) 136 mcg, with indacaterol (IND) 114 mcg and glycopyrronium (GLY) 46 mcg was reasonable. However, the PBAC considered for purposes of satisfying Section 101(3B) of the *National Health Act 1953*, any high dose inhaled corticosteroid (ICS) with long-acting beta2-agonist (LABA) + tiotropium (TIO) combination are relevant alternative therapies. The PBAC's recommendation was therefore, among other matters, based on its assessment that the cost of FF/UMEC/VI should be no greater than the lowest price combination of the PBS listed components of triple therapy that are available for asthma at comparable doses.

7.3 The PBAC noted the input from organisations and health care professionals supporting the listing of FF/UMEC/VI for severe asthma.

7.4 The PBAC considered MF/IND/GLY 136/114/46 to be an appropriate comparator. In addition, the PBAC also considered that high dose ICS/LABA FDCs + TIO were appropriate alternative therapies.

7.5 The PBAC noted that the claim of non-inferior effectiveness for FF/UMEC/VI compared to MF/IND/GLY and high dose ICS/LABA FDCs + TIO was based on indirect comparisons using the CAPTAIN, PrimoTinA, IRIDIUM, ARGON and TRIGGER trials. The PBAC noted the transitivity concerns raised (see paragraph 6.12), but considered the populations studied across the identified trials were broadly comparable. The PBAC acknowledged the inclusion of patients with no severe exacerbation in the previous 12 months in the CAPTAIN trial was an exception, but considered the sub-group data presented

accounted for differences in severe exacerbations prior to enrolment. The PBAC agreed with the ESC that it was reasonable, based on prior PBAC decisions, to rely predominantly on the primary outcome (FEV1) for the purposes of assessing non-inferiority. The PBAC agreed with the ESC that the FEV1 evidence presented in the submission supported the claim of non-inferior efficacy.

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

7.7 The PBAC noted that the submission presented a cost-minimisation analysis between FF/UMEC/VI and the main comparator MF/IND/GLY 136/114/46, and versus high dose ICS/LABA + TIO. The PBAC considered that the cost-minimisation analysis should be against the least costly triple therapy combination of either MF/IND/GLY 136/114/46 or high dose ICS/LABA + TIO that provided a treatment duration of 30 days at the equi-effective doses outlined in paragraph 6.40 and Table 9.

7.8 The PBAC noted the concerns raised with the financial estimates regarding the potential for use in less severe asthma (see paragraph 6.48). In addition, the PBAC noted concerns regarding inappropriate use of FF/UMEC/VI in children and adolescents (see paragraph 3.3). While these risks may be reduced by the implementation of an Authority Required (telephone/online) listing, the PBAC considered the inconsistencies created in the restriction authority type between single inhaler triple therapies across COPD and severe asthma may not be appropriate (see paragraph 3.3). As such, the PBAC recommended an Authority Required (STREAMLINED) listing for FF/UMEC/VI for severe asthma. The PBAC considered the circumstances of PBS eligibility applicable to single inhaler triple therapy FDCs for severe asthma should be consistent and as such flow-on restriction changes would also be required for MF/IND/GLY as outlined in paragraph 8.2.

7.9 The PBAC recommended that DUSC undertake a review of utilisation of single inhaler triple therapies for severe asthma after an appropriate period post listing with a view to reversion to Authority Required (telephone /online) if use beyond the intent of the restriction is evident.

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

7.11 The PBAC advised that FF/UMEC/VI is suitable for prescribing by nurse practitioners.

7.12 The PBAC recommended that the Early Supply Rule should apply to FF/UMEC/VI.

7.13 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because FF/UMEC/VI 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.

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

Outcome:
Recommended

8 Recommended listing

8.1 Add new medicinal product pack (new strength; 200 mcg-62.5mcg-25 mcg) 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
FLUTICASONE FUROATE + UMECLIDINIUM + VILANTEROL						
fluticasone furoate 200 microgram/actuation + umeclidinium 62.5 microgram/actuation + vilanterol 25 microgram/actuation powder for inhalation, 30 actuations		NEW	1	30	5	Trelegy Ellipta 200/62/5/25
Restriction Summary New 1 / Treatment of Concept: New 2						
	Category / Program: GENERAL – General Schedule (Code GE)					
	Prescriber type: ☒Medical Practitioners ☒Nurse practitioners					
	Restriction type: ☒Authority Required (STREAMLINED) [New 2 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 pharmaceutical benefit is not for the treatment of chronic obstructive pulmonary disease (COPD)					
	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.					

8.2 Flow on changes:

Update the indacaterol + gylcopyrronium + mometasone (Enerzair Breezhaler) restriction (excluding the administrative advice where New AA1/10615 are different) to be the same as that appearing above, by:

(1) Amending the restriction type from 'Authority Required (telephone/online PBS authorities system) to 'Authority Required (STREAMLINED); and

(2) Inserting and removing the relevant restriction concepts (25796 & 18275/New CC1).

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
INDACATEROL + GLYCOPYRRONIUM + MOMETASONE					
indacaterol 114 microgram + glycopyrronium 46 microgram + mometasone furoate 68 microgram, powder for inhalation, 30 capsules	12298G	1	30	5	Enerzair Breezhaler
indacaterol 114 microgram + glycopyrronium 46 microgram + mometasone furoate 136 microgram, powder for inhalation, 30 capsules	12295D	1	30	5	Enerzair Breezhaler

Edit Restriction Summary 11470 / Treatment of Concept: 11470 (current as at 1 November 2021) to become: ***Restriction Summary New 1 / Treatment of Concept: New 2***	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners ☒Nurse practitioners
	Restriction type: ☒ Authority Required ~~(telephone/online PBS Authorities system)~~ *(STREAMLINED) [New 2 code]*
	~~**Administrative Advice:**~~ ~~Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.~~
	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
	~~**AND**~~
	Population criteria:
	Patient must be aged 18 years or older
	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 drug is not PBS-subsidised for the treatment of chronic obstructive pulmonary disease (COPD).
	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.

Update the first clinical criterion in tiotropium's severe asthma listing to match the above updates, for the reason outlined at paragraph 3.4, as follows (only relevant section shown):

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
TIOTROPIUM					
tiotropium 2.5 microgram/actuation inhalation solution, 60 actuations	11043F	1	1	5	Spiriva Respimat
Edit Restriction Summary 8545 / Treatment of Concept: 8605 *(current as at 1 November 2021) to become:*					
	Category / Program: GENERAL – General Schedule (Code GE)				
	Restriction type: ☒ Restricted Benefit				
	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				

The flow on changes would be applied at the same time as listing the new product or prior (should the listing not proceed).

These restrictions may be subject to further review. Should there be any changes made to the restrictions the sponsors will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in

relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

GSK welcomes the PBAC recommendation to list Trelegy Ellipta 200 (fluticasone furoate/umeclidinium/vilanterol) on the PBS for the treatment of severe asthma.