5.03 FLUTICASONE FUROATE 100 mcg + UMECLIDINIUM 62.5 mcg + VILANTEROL 25 mcg, powder for inhalation, 30 actuations, Trelegy® Ellipta®, GlaxoSmithKline Australia

1 Purpose of application

1.1 The submission requested a Section 85, Authority Required (STREAMLINED) listing for fluticasone furoate 100 mcg with umeclidinium 62.5 mcg and vilanterol 25 mcg (Trelegy®) for the treatment of patients with chronic obstructive pulmonary disease (COPD). The PBAC has not previously considered Trelegy.

1.2 The listing was requested on the basis of a cost-minimisation analysis versus fluticasone propionate 500 mcg/salmeterol 50 mcg fixed dose combination (FDC) twice daily plus tiotropium 18 mcg once daily as a proxy for all inhaled corticosteroid (ICS), long-acting beta2 agonist (LABA) and long-acting muscarinic antagonist (LAMA) combinations and a cost-consequence analysis versus any LAMA/LABA FDC.

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

Component	Description
Population	Patients with moderate to severe COPD (FEV_1 < 50% predicted) and frequent exacerbations despite maintenance therapy
Intervention	Fluticasone furoate 100 mcg/umeclidinium 62.5 mcg/vilanterol 25 mcg FDC (Trelegy®) one inhalation daily
Comparator	ICS/LABA + LAMA (fluticasone propionate 500 mcg/salmeterol 50 mcg FDC one inhalation twice daily + tiotropium 18 mcg one inhalation daily) OR LAMA/LABA FDCs (tiotropium 2.5 mcg/olodaterol 2.5 mcg two inhalations daily; indacaterol 110 mcg/glycopyrronium 50 mcg one inhalation daily; umeclidinium 62.5 mcg/vilanterol 25 mcg one inhalation daily; aclidinium 340 mcg/eformoterol 12 mcg one inhalation twice daily)
Outcomes	Improved lung function, reduced frequency of exacerbations, improved quality of life and decreased use of rescue medications
Clinical claim	Any triple therapy combination of fluticasone furoate 100 mcg, umeclidinium 62.5 mcg and vilanterol 25 mcg (Trelegy or FDC and single agent combination) is noninferior in terms of efficacy and safety compared with fluticasone propionate 500 mcg/salmeterol 50 mcg FDC one inhalation twice daily + tiotropium 18 mcg one inhalation daily Any triple therapy combination of fluticasone furoate 100 mcg, umeclidinium 62.5 mcg and vilanterol 25 mcg (Trelegy or FDC and single agent combination) is superior in terms of efficacy and noninferior in terms of safety compared to LAMA/LABA combination therapy

Abbreviations: COPD, chronic obstructive pulmonary disease; FDC, fixed dose combination; FEV_1, forced expiratory volume in one second; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist
Source: Table 1 (p 18) of the submission

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
FLUTICASONE FUROATE + UMECLIDINIUM + VILANTEROL Fluticasone furoate 100 microgram/actuation + umeclidinium 62.5 microgram/actuation + vilanterol 25 microgram/actuation	1	5	$[redacted]	Trelegy® Ellipta® GSK

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☒ Nurse practitioners ☐ Optometrists ☐ Midwives
Episodicity:	-
Severity:	-
Condition:	Chronic Obstructive Pulmonary Disease
PBS Indication:	Chronic Obstructive Pulmonary Disease
Treatment phase:	~~Maintenance treatment~~
Restriction Level / Method:	☐ Restricted benefit ☐ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required - Emergency ☐ Authority Required - Electronic ☒ Streamlined
Treatment criteria:	~~This product is not PBS subsidised for the treatment of asthma.~~ ~~This product is not indicated for the initiation of bronchodilator therapy in COPD.~~ ~~The treatment must not be used in combination with an ICS/LABA, LABA/LAMA or LAMA or LABA monotherapy.~~ ~~A LAMA includes tiotropium, glycopyrronium, aclidinium or umeclidinium.~~ ~~A LABA includes olodaterol, indacaterol, salmeterol, eformoterol or vilanterol.~~ ~~An ICS includes fluticasone propionate, fluticasone furoate, budesonide, beclomethasone or ciclesonide.~~
Clinical criteria:	Patient must have a forced expiratory volume in 1 second (FEV_1) less than 50% of predicted normal prior to therapy AND Patient must have a history of repeated exacerbations with significant symptoms despite regular long-acting bronchodilator therapy.
Population criteria:	~~Patients must be aged 18 years or older~~
Foreword	-
Definitions	-
Prescriber Instructions	-
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. *Diagnosis of COPD should be confirmed with spirometry.* *This product is not PBS-subsidised for the treatment of asthma.* *This product is not indicated for the initiation of bronchodilator therapy in COPD.* *The treatment must not be used in combination with an ICS/LABA, LABA/LAMA or LAMA, LABA or ICS monotherapy.*

	A LAMA includes tiotropium, glycopyrronium, aclidinium or umeclidinium. *A LABA includes olodaterol, indacaterol, salmeterol, eformoterol or vilanterol.* *An ICS includes fluticasone propionate, fluticasone furoate, budesonide, beclomethasone or ciclesonide.*
Cautions	-

2.2 The requested restriction is narrower than the requested TGA indication as the proposed FEV1 threshold and repeated exacerbations despite bronchodilator therapy indicate a more severe condition. There is a high risk of use outside the restriction in patients with only one of the two clinical criteria (i.e. FEV1 less than 50% predicted normal or repeated exacerbations). DUSC considered that the proposed clinical criteria limiting use to patients with an FEV1 <50% predicted normal would not limit inappropriate use of triple therapy, particularly given low levels of spirometry testing performed in general practice1 and the accuracy of tests in determining disease severity. There is also potential for off-label use in patients with asthma.

2.3 The requested restriction does not appear to limit use of Trelegy to patients failing dual therapy, which is inconsistent with treatment guidelines recommending a stepwise approach and the proposed place in therapy in patients failing ICS/LABA or LAMA/LABA combination therapy. The Pre-Sub-Committee Response (PSCR, p2) considered that Trelegy may be an appropriate clinical option in patients with more severe disease requiring urgent escalation from monotherapy to triple therapy.

2.4 DUSC noted that the proposed restriction level (Authority Required Streamlined) was the same as for LAMA/LABA dual therapy and was also recently recommended for ICS/LABA treatment for COPD. The restriction level was therefore not a distinguishing feature of triple therapy; however, it is unlikely to be feasible to further increase the restriction level in a population of this size.

2.5 The ESC considered that the restriction wording could be modified to explicitly note that all other LAMA, LABA or ICS containing inhalers must be ceased on commencement of Trelegy. This is in response to QUM concerns that Trelegy could be incorrectly used with other LAMA, LABA or ICS inhalers, or with other FDCs.

2.6 DUSC and ESC both reiterated that assessment of inhaler technique is particularly important to limit premature escalation of treatment to triple therapy in situations where poor treatment response is due to inappropriate device use.

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

3 Background

Registration status

3.1 The submission was made under TGA/PBAC Parallel Process. The TGA Delegate recommended that the indication state that "Trelegy Ellipta is indicated for the maintenance treatment of adults with moderate to severe COPD who require treatment with LAMA/LABA and ICS. Trelegy Ellipta is not indicated for the initiation of therapy in COPD."

[1] Post-market Review of COPD medicines, Draft Report. Available at: http://www.pbs.gov.au/reviews/copd-public-consult-files-pages/1-executive-summary-public-consultation.pdf

4 Population and disease

4.1 Chronic obstructive pulmonary disease (COPD) is characterised by chronic inflammation of the lung tissue causing a mixture of small airways narrowing and emphysema leading to airflow limitation. Patients most commonly present with shortness of breath, chronic cough and sputum production. Less common symptoms include wheezing and chest tightness. Worsening of symptoms by irritants such as infection or exposure to noxious particles or gases (most commonly cigarette smoke) can result in exacerbations, hospitalisations and death. COPD is a progressive disease that occurs over many years and mostly affects middle aged and older people. It is commonly associated with multiple co-morbidities (e.g. lung cancer, cardiovascular disease, osteoporosis, skeletal muscle dysfunction, metabolic syndrome, anxiety, depression and cognitive dysfunction). The most important risk factor for COPD is cigarette smoking and passive exposure to cigarette smoke.

4.2 The target population in the submission is patients with moderate to severe COPD (FEV_1 < 50% predicted) and frequent exacerbations (2 or more within a 12 month period) despite maintenance therapy.

4.3 Treatment guidelines for COPD generally recommend a stepwise approach for moderate to severe patients (based on symptoms and exacerbation frequency) with initial treatment with LABA or LAMA monotherapy, followed by dual therapy LAMA/LABA, followed by a switch to ICS/LABA or triple therapy ICS/LABA/LAMA. The draft report of the Post-market Review of COPD medicines (p10) notes that a recent Cochrane Review found that LAMA/LABA treatment was associated with greater improvements in FEV_1, fewer exacerbations, more frequent improvement in quality of life and lower risk of pneumonia compared to ICS/LABA treatment.

4.4 The submission positions Trelegy as triple therapy ICS/LAMA/LABA in patients with exacerbations or who remain symptomatic despite dual therapy with a LAMA/LABA or ICS/LABA.

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

5 Comparator

5.1 The submission nominated a triple therapy combination of fluticasone propionate 500 mcg/salmeterol 50 mcg FDC plus tiotropium 18 mcg and dual therapy of any LAMA/LABA FDC as main comparators. The ESC considered that the comparators were appropriate as a proxy for a range of treatment combinations.

5.2 In triple therapy, any ICS (e.g. beclomethasone, budesonide, ciclesonide, fluticasone propionate, fluticasone furoate), LABA (e.g. eformoterol, indacaterol, salmeterol, vilanterol) and LAMA (aclidinium, glycopyrronium, tiotropium, umeclidinium) combination could potentially be substituted by Trelegy.

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 (2) via the Consumer Comments facility on the PBS website. The comments described concerns about the over-prescribing of ICS for people with COPD, particularly in relation to increased risk of osteoporotic fracture, diabetes and pneumonia.

Clinical trials

6.3 The submission was based on a series of comparisons:

Triple therapy vs triple therapy

- Indirect comparison of triple therapy combinations including fluticasone furoate, umeclidinium and vilanterol (Trelegy FDC in FULFIL; fluticasone furoate/vilanterol FDC plus umeclidinium in Trials 200109 and 200110) compared to triple therapy with fluticasone propionate/salmeterol FDC plus tiotropium (GLISTEN, Cazzola 2007) using ICS/LABA fixed dose combinations as the common reference arm.

Triple therapy vs dual therapy

- Indirect comparison of triple therapy combinations including fluticasone furoate, umeclidinium and vilanterol (Trelegy FDC in FULFIL; fluticasone furoate/vilanterol FDC plus umeclidinium in Trials 200109 and 200110) compared to LAMA/LABA FDC (AFFIRM, FLAME, ILLUMINATE, LANTERN, DB2116134) using ICS/LABA fixed dose combinations as the common reference arm.
- Supportive indirect comparison of any triple therapy combination including an ICS, LAMA and LABA (FULFIL, Trial 200109, Trial 200110, GLISTEN, Cazzola 2007, Trial 201314) compared to LAMA/LABA FDC (FLAME, ILLUMINATE, LANTERN, DB2116134) using ICS/LABA fixed dose combinations as the common reference arm.
- Supportive direct comparison of triple therapy with fluticasone propionate/salmeterol FDC plus tiotropium compared to LAMA/LABA FDC (Aaron 2007).
- IMPACT was a large head-to-head study comparing Trelegy to fluticasone furoate/vilanterol FDC (ICS/LABA) and umeclidinium/vilanterol FDC (LAMA/LABA). The full trial results from IMPACT were provided with the PSCR, however these were not evaluated as they were submitted beyond the submission deadline. The IMPACT trial is likely to provide the most reliable comparison of triple therapy to LAMA/LABA or ICS/LABA dual therapy.
- Direct comparisons of Trelegy versus ICS/LABA FDC (FULFIL trial) were also included for further consideration during the evaluation.

6.4 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
Trelegy trials		
FULFIL	GSK Clinical Study Report (2016). A Phase III, 24 week, randomised, double blind, double dummy, parallel group study (with an extension to 52 weeks in a subset of subjects) comparing the efficacy, safety and tolerability of the fixed dose triple combination FF/UMEC/VI administered once daily in the morning via a dry powder inhaler with budesonide/formoterol 400mcg/12mcg administered twice-daily via a reservoir inhaler in subjects with chronic obstructive pulmonary disease	Internal study report
	Lipson DA et al (2017). FULFIL Trial: Once-Daily Triple Therapy in Patients with Chronic Obstructive Pulmonary Disease.	American Journal of Respiratory and Critical Care Medicine 196: 438-446
	Lipson DA et al (2017). Single-inhaler triple therapy in advanced COPD patients: prior medication and disease severity FULFIL subanalyses	Poster No. PA1057. ERS International Congress, September 2017
IMPACT	Pascoe SJ et al (2016). A phase III randomised controlled trial of single-dose triple therapy in COPD: the IMPACT protocol	European Respiratory Journal 48: 320-330
	GSK press release (2017). GSK and Innoviva report positive headline results from IMPACT study showing single inhaler triple therapy Trelegy Ellipta reduced COPD exacerbations	Press release (20 September 2017)
ICS, LAMA, LABA triple therapy combination trials		
Trial 200109	GSK Clinical Study Report (2014). A study to compare the addition of umeclidinium bromide (UMEC) to fluticasone furoate (FF)/vilanterol (VI), with placebo plus FF/VI in subjects with Chronic Obstructive Pulmonary Disease (COPD).	Internal study report
	Siler TM et al (2015). Efficacy and safety of umeclidinium added to fluticasone furoate/vilanterol in chronic obstructive pulmonary disease: Results of two randomized studies	Respiratory Medicine 109: 1155-1163.
Trial 200110	GSK Clinical Study Report (2014). A study to compare the addition of umeclidinium bromide (UMEC) to fluticasone furoate (FF)/vilanterol (VI), with placebo plus FF/VI in subjects with Chronic Obstructive Pulmonary Disease (COPD).	Internal study report
	Siler TM et al (2015). Efficacy and safety of umeclidinium added to fluticasone furoate/vilanterol in chronic obstructive pulmonary disease: Results of two randomized studies	Respiratory Medicine 109: 1155-1163.
Trial 201314	GSK Clinical Study Report (2015). A randomized, parallel group study to evaluate the effect of Umeclidinium (UMEC) added to inhaled corticosteroid/long acting beta-agonist combination therapy in subjects with Chronic Obstructive Pulmonary Disease (COPD).	Internal study report
	Sousa AR et al (2016). The effect of umeclidinium added to inhaled corticosteroid/long-acting beta2-agonist in patients with symptomatic COPD: a randomised, double-blind, parallel-group study.	NPJ Primary Care Respiratory Medicine 26: 16031
GLISTEN	Frith PA et al (2015). Glycopyrronium once-daily significantly improves lung function and health status when combined with salmeterol/fluticasone in patients with COPD: the GLISTEN study, a randomised controlled trial.	Thorax 70: 519-27
Aaron (2007)	Aaron SD et al (2007). Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial.	Annals of Internal Medicine, 146(8): 545-55

Trial ID	Protocol title/ Publication title	Publication citation
Cazzola (2007)	Cazzola M et al (2007). A pilot study to assess the effects of combining fluticasone propionate/salmeterol and tiotropium on the airflow obstruction of patients with severe-to-very severe COPD.	Pulmonary Pharmacology & Therapeutics, 20(5): 556-61
LAMA/LABA FDC trials		
AFFIRM	Vogelmeier CF et al (2016). Efficacy and safety of aclidinium/formoterol versus salmeterol/fluticasone: a phase 3 COPD study.	European Respiratory Journal, 48: 972-975
FLAME	Wedzicha JA et al (2016). Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD.	New England Journal of Medicine, 374(23): 2222-2234
	Wedzicha JA et al (2017). Indacaterol/glycopyrronium versus salmeterol/fluticasone in Asian patients with COPD at a high risk of exacerbations: results from the FLAME study	International Journal of Chronic Obstructive Pulmonary Disease, 12339-349
ILLUMINATE	Vogelmeier CF et al (2013). Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol-fluticasone in patients with chronic obstructive pulmonary disease (ILLUMINATE): a randomised, double-blind, parallel group study.	The Lancet Respiratory Medicine, 1(1): 51-60
LANTERN	Zhong N et al (2015). LANTERN: a randomized study of QVA149 versus salmeterol/fluticasone combination in patients with COPD.	International Journal of Chronic Obstructive Pulmonary Disease, 101015-26
	Zhong N et al (2016). Efficacy and Safety of Indacaterol/Glycopyrronium (IND/GLY) Versus Salmeterol/Fluticasone in Chinese Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease: The Chinese Cohort from the LANTERN Study.	COPD: Journal of Chronic Obstructive Pulmonary Disease, 13(6): 686-692
DB2116134	Singh D et al (2015). Umeclidinium/vilanterol versus fluticasone propionate/salmeterol in COPD: a randomised trial.	BMC Pulmonary Medicine, 1591

Source: Table 13 (p 43-47) of the submission
Note: Abstracts of studies with full publications are not presented

6.5 The key features of the included trials are summarised in the table below.

Table 3: Key features of the included evidence

Trial (comparison)	N	Design/ duration of follow-up	Risk of bias	Patient population	Primary outcome
Trelegy trials					
FULFIL	1,810	MC, R, DB, DD, SUP (24 week trial with extension to 52 weeks)	Low	Moderate COPD with exacerbations or severe COPD	Change in trough FEV_1, change in SGRQ
IMPACT	10,335	MC, R, DB, SUP (52 weeks)	Unclear	Moderate/severe COPD with exacerbations	Annual rate of exacerbations
ICS, LAMA, LABA triple therapy combinations					
Trial 200109	619	MC, R, DB, SUP (12 weeks)	Low	Moderate/severe COPD	Change in trough FEV_1
Trial 200110	620	MC, R, DB, SUP (12 weeks)	Low	Moderate/severe COPD	Change in trough FEV_1
Trial 201314	236	MC, R, DB, SUP (12 weeks)	Low	Moderate/severe COPD	Change in trough FEV_1
GLISTEN	773	MC, R, DB, SUP (12 weeks)	Unclear	Moderate/severe COPD	Change in trough FEV_1
Aaron (2007)	449	MC, R, DB, DD, SUP (52 weeks)	Unclear	Moderate/severe COPD	Proportion of patients with exacerbations
Cazzola (2007)	90	MC, R, DB, DD (12 weeks)	Low	Severe COPD	Change in trough FEV_1
LAMA/LABA FDC trials					
AFFIRM	933	MC, R, DB, DD, SUP (24 weeks)	Low	Moderate/severe COPD	Change in peak FEV_1
FLAME	3,362	MC, R, DB, DD, NI (52 weeks)	Low	Moderate/severe COPD	Annual rate of exacerbations
ILLUMINATE	523	MC, R, DB, DD, SUP (26 weeks)	Low	Moderate/severe COPD	Change in $AUC_{0\text{-}12h}$ FEV_1
LANTERN	744	MC, R, DB, DD, NI (26 weeks)	Low	Moderate/severe COPD	Change in trough FEV_1
DB2116134	717	MC, R, DB, DD, SUP (12 weeks)	Low	Moderate/severe COPD	Change in weighted mean FEV_1

Abbreviations: AUC, area under the curve; COPD, chronic obstructive pulmonary disease; DB, double blind; DD, double-dummy; FEV_1, forced expiratory volume in one second; MC, multi-centre; NI, noninferiority, R, randomised; SUP, superiority
Source: compiled during the evaluation

6.6 The submission acknowledged potential differences in age, baseline FEV_1 and exacerbation history between clinical trials and the proposed PBS population. However, the submission argued that these differences were unlikely to have a substantial impact on comparative results. This was not reasonable as the proposed PBS population represents a more severe patient group than the clinical trial population and the available subgroup analyses suggest smaller improvements in more severe populations.

6.7 It was also unclear whether the use of prior therapies and degree of asthma/COPD overlap in the clinical trial populations was representative of the proposed PBS population. Post-hoc subgroup analyses suggest that use of prior therapies is likely to

affect treatment efficacy estimates. The impact of airway reversibility (i.e. asthma-like symptoms) was not adequately addressed in the submission.

Comparative effectiveness

Triple therapy vs triple therapy (indirect)

6.8 The results of the indirect comparison between triple therapy combinations containing fluticasone furoate, vilanterol, umeclidinium (Trelegy or fluticasone furoate/vilanterol FDC plus umeclidinium) and triple therapy with fluticasone propionate/salmeterol plus tiotropium are summarised in the table below.

Table 4: Summary of indirect analyses comparing triple therapy with fluticasone furoate, vilanterol, umeclidinium vs. triple therapy with fluticasone propionate, salmeterol, tiotropium

Outcome	Time point	Base case result (95% CI)
Change from baseline in trough FEV_1 (mL) [Results > 0 favour FF/VI/UMEC]	12 weeks	**Mean difference:** [redacted]
Change from baseline in SGRQ total Score [Results < 0 favour FF/VI/UMEC]	12 weeks	Mean difference: 1.67 (-0.64, 3.97)
Change from baseline in rescue medication use (puffs per day) [Results < 0 favour FF/VI/UMEC]	12 weeks	Mean difference: [redacted]
Proportion of subjects experiencing ≥1 moderate/severe exacerbation [Results < 1 favour FF/VI/UMEC]	12 weeks	Odds ratio: [redacted]

Abbreviations: CI, confidence interval; FDC, fixed dose combination; FEV_1, forced expiratory volume in one second; FF, fluticasone furoate; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; SGRQ, St George Respiratory questionnaire; UMEC, umeclidinium; VI, vilanterol
Source: Table 74 (p 191) of the submission
Bolding indicates statistically significant results

6.9 The results of the indirect comparisons suggest that there were no clinically important differences between triple therapy combination containing fluticasone furoate, vilanterol and umeclidinium, and triple therapy combinations containing fluticasone propionate, salmeterol, and tiotropium.

6.10 The submission acknowledged differences in patient populations between trials with variation in the number of patients with severe COPD (20-100%), mean baseline predicted FEV1 (40-60%), current smokers (25-80%), exacerbation history (0-100%) and degree of reversibility (10-25%). It was unclear whether trials were sufficiently similar to justify their inclusion in presented meta-analyses and indirect comparisons.

Triple therapy vs LAMA/LABA (indirect)

6.11 The results of the indirect comparison between triple therapy combinations containing fluticasone furoate, vilanterol, umeclidinium (Trelegy or fluticasone furoate/vilanterol FDC plus umeclidinium) and LAMA/LABA FDC are summarised in the table below.

Table 5: Summary of indirect analyses comparing triple therapy with fluticasone furoate, vilanterol, umeclidinium vs. LAMA/LABA FDC

Outcome	Time point	Base case result (95% CI)
Change from baseline in trough FEV_1 (mL) [Results > 0 favour FF/VI/UMEC]	12 weeks	**Mean difference:** [redacted]
	24/26 weeks	**Mean difference: 109 (48, 171)**
	52 weeks	**Mean difference: 117 (67, 167)**
Proportion of trough FEV_1 responders (patients with ≥ 100 mL increase from baseline) [Results > 1 favour FF/VI/UMEC]	12 weeks	**Odds ratio:** [redacted]
	24/26 weeks	**Odds ratio: 1.71 (1.18, 2.48)**
Change from baseline in SGRQ total Score [Results < 0 favour FF/VI/UMEC]	12 weeks	Mean difference: -1.20 (-2.89, 0.48)
	24/26 weeks	Mean difference: -1.69 (-3.39, 0.02)
	52 weeks	Mean difference: -1.40 (-4.35, 1.55)
Proportion of SGRQ responders (patients with ≥ 4 point decrease from baseline) [Results > 1 favour FF/VI/UMEC]	12 weeks	Odds ratio: 1.52 (0.81, 2.84)
	24/26 weeks	Odds ratio: 1.35 (0.89, 2.04)
	52 weeks	Odds ratio: 1.20 (0.79, 1.83)
Change from baseline in rescue medication use (puffs per day) [Results < 0 favour FF/VI/UMEC]	12 weeks	Mean difference: [redacted]
	24/26 weeks	Mean difference: -0.01 (-0.37, 0.35)
	52 weeks	Mean difference: [redacted]
Moderate/severe exacerbation rate [Results < 1 favour FF/VI/UMEC]	24/26 weeks	Rate ratio: 0.79 (0.59, 1.07)
	52 weeks	Rate ratio: 0.68 (0.44, 1.03)
Proportion of subjects experiencing ≥1 moderate/severe exacerbation [Results < 1 favour FF/VI/UMEC]	12 weeks	**Odds ratio:** [redacted]
	24/26 weeks	Odds ratio: 0.89 (0.58, 1.40)

Abbreviations: CI, confidence interval; FDC, fixed dose combination; FEV_1, forced expiratory volume in one second; FF, fluticasone furoate; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; SGRQ, St George Respiratory questionnaire; UMEC, umeclidinium; VI, vilanterol
Source: Table 91 (p 221-222) of the submission
Bolding indicates statistically significant results

6.12 The results of the indirect comparison suggest that treatment with Trelegy may be associated with improvements in lung function (MCID 100 mL) compared to LAMA/LABA FDC but appeared to have a limited impact on functional symptoms (MCID 4 points) and rescue medication use (no MCID, small reduction) as well as an unclear impact on exacerbations (inconsistent results). This was consistent with the results of the supportive indirect comparisons comparing any triple therapy combination to LAMA/LABA, while the supportive direct comparison of fluticasone propionate/salmeterol FDC plus tiotropium to LAMA/LABA FDCs suggested that triple therapy regimens may be associated with improvements in exacerbations but appeared to have limited impact on lung function, functional symptoms and rescue medication use.

6.13 The submission acknowledged differences in patient populations between trials with variation in the number of patients with severe COPD (20-100%), mean baseline predicted FEV1 (40-60%), current smokers (25-80%), exacerbation history (0-100%) and degree of reversibility (10-25%). It was unclear whether trials were sufficiently similar to justify their inclusion in presented meta-analyses and indirect comparisons.

6.14 The submission did not adequately justify methodological approaches used in the indirect analyses, including the selected pooling of different time points for some

outcomes as well as comparing change from baseline measures with endpoint measures.

Triple therapy vs dual therapy (IMPACT trial)

6.15 The unedited IMPACT trial data tables were provided as part of the PSCR. Results of the direct comparison between Trelegy and dual therapy (both ICS/LABA FDC and LAMA/LABA FDC) are summarised in the table below. The ESC did not consider these data as they were submitted well after the submission deadline and have not been independently evaluated.

Table 6: Comparison of FF/UMEC/VI to FF/VI and UMEC/VI in the IMPACT trial

	FF/UMEC/VI	FF/VI	UMEC/VI
Exacerbations			
Annual rate of on-treatment moderate/severe exacerbations (95% CI)	0.91 [redacted]	1.07 [redacted]	1.21 [redacted]
Percentage reduction in annual moderate/severe exacerbations between FF/UMEC/VI and column		15% [redacted] p<0.001	25% [redacted] p<0.001
Lung function			
Patients obtaining at least 100 mL increase from baseline in trough FEV_1 at 52 weeks	[redacted]	[redacted]	[redacted]
Treatment difference in patients obtaining ≥100 mL increase in trough FEV_1 between FF/UMEC/VI and column		[redacted]	[redacted]

Abbreviations: FF, fluticasone furoate; VI, vilanterol; UMEC, umeclidinium; OR, odds ratio;
Source: Tables 1 and 2, PSCR p1-2, and Table 2.049 of IMPACT study tables

6.16 It was noted that the results of the IMPACT trial suggest that treatment with Trelegy may be associated with improvements in exacerbations and lung function compared to ICS/LABA FDC and LAMA/LABA FDC. High level results provided with the evaluation indicated limited impact on functional symptoms and rescue medication use.

6.17 Due to the limited documentation available for the IMPACT trial during the evaluation, the reported data should be interpreted with caution.

6.18 The results of the direct comparison of Trelegy versus LAMA/LABA FDC in the IMPACT trial indicated more modest improvements than estimated in the indirect analysis, with an improvement in trough FEV_1 at 52 weeks over UMEC/VI of 54 mL (95% CI 39 mL, 69 mL) and over FF/VI of 97 mL (95% CI 85 mL, 109 mL).

6.19 Patients in the IMPACT trial were required to be on prior maintenance therapy which was discontinued on the day before receiving trial treatments. This study design may confound the interpretation of results. The PSCR (p3) considered that this feature of the study reflects real world use and is therefore applicable to the general population.

Triple therapy vs ICS/LABA (FULFIL trial)

6.20 The results of the direct comparison between Trelegy and ICS/LABA FDC in the FULFIL trial are summarised in the table below.

Table 7: Comparison of key outcomes reported for FF/UMEC/VI FDC (Trelegy) vs BUD/EFOR FDC (Symbicort) in the FULFIL trial

Outcome	FF/UMEC/VI FDC (Trelegy) N = 911	BUD/EFOR FDC (Symbicort) N = 899	Treatment difference
Spirometry outcomes			
Baseline trough FEV_1 (mL), mean (SD)	[redacted]	[redacted]	-
Change in trough FEV_1 (mL) at 12 weeks, LSM (SE)	[redacted]	[redacted]	[redacted]
Change in trough FEV_1 (mL) at 24 weeks, LSM (SE) [primary outcome]	142 (8.3)	-29 (8.5)	**171 (95% CI 148, 194)**
Change in trough FEV_1 (mL) at 52 weeks, LSM (SE) [extension]	126 [redacted] N = 210	-53 [redacted] N = 220	**179 (95% CI 131, 226)**
Proportion of responders (change in trough $FEV_1 \geq 100$ mL) at 12 weeks	[redacted]	[redacted]	[redacted]
Proportion of responders (change in trough $FEV_1 \geq 100$ mL) at 24 weeks	453/907 (49.9%)	184/892 (20.6%)	**OR 4.03 (95% CI 3.27, 4.97)**
Proportion of responders (change in trough $FEV_1 \geq 100$ mL) at 52 weeks [extension]	96/210 (45.7%)	34/219 (15.5%)	**OR 4.79 (95% CI 3.02, 7.61)**
Functional symptom measures[a,b]			
Baseline SGRQ score, mean (SD)	51.8 (16.3)	50.8 (16.7)	-
Change in SGRQ at 24 weeks, LSM (SE) [primary outcome]	-6.6 (0.45)	-4.3 (0.46)	**-2.2 (-3.5, -1.0)**
Change in SGRQ at 52 weeks, LSM (SE) [extension]	-4.6 [redacted] N = 210	-1.9 [redacted] N = 220	**-2.7 (-5.5, 0.2)**
Proportion of responders (change in score ≥ 4) at 24 weeks	448/904 (50.0%)	368/893 (41.2%)	**OR 1.41 (95% CI 1.16, 1.70)**
Proportion of responders (change in score ≥ 4) at 52 weeks [extension]	91/209 (43.5%)	73/219 (33.3%)	**OR 1.50 (95% CI 1.01, 2.24)**
Rescue medication use			
Baseline puffs per day, mean (SD)	[redacted]	[redacted]	-
Change in puffs per day at 12 weeks, LSM (SE)	[redacted]	[redacted]	[redacted]
Change in puffs per day at 24 weeks, LSM (SE)	-0.1 (0.04)	0.1 (0.04)	**-0.2 (-0.3, -0.1)**
Change in puffs per day at 52 weeks, LSM (SE) [extension]	[redacted]	[redacted]	[redacted]
Exacerbation			
Mean annual moderate/severe exacerbation rate at 24 weeks	0.22	0.34	**RR 0.65 (0.49, 0.86)**
Mean annual moderate/severe exacerbation rate at 52 weeks	0.20 N = 210	0.40 N = 220	**RR 0.56 (0.37, 0.85)**

Abbreviations: BUD, budesonide; CI, confidence interval; EFOR, eformoterol; FDC, fixed dose combination; FF, fluticasone furoate; LSM, least squares mean; NR, not reported; OR, odds ratio; RR, rate ratio; SD, standard deviation; SE, standard error; SGRQ, St George Respiratory questionnaire; TDI, TDI, transition dyspnoea index; VI, vilanterol; UMEC, umeclidinium

Source: Table 33 (p 121-122), Table 34 (p 123-124), Table 35 (p 124); Table 36 (p 126), Table 38 (p 131), Table 39 (p 132), Table 40 (p 134-135), Table 42 (p 138), Table 43 (p 139), Table 44 (p 141), Table 45 (p 143-144), Table 46 (p 145), Table 47 (p 146-147), Table 48 (p 148) of the submission; Table 20 (p 93), Table 26 (p 106), Table 28 (p 109), Table 39 (p 132), Table 41 (p 134), Table 52 (p 146), Table 2.016 (p 910) of the FULFIL trial report. Bolding indicates statistically significant results

[a] SGRQ is a functional symptom measure with a 0-100 scale with higher values indicating worse symptoms

[b] TDI is a functional symptoms measure with a -9 to + 9 scale with higher values indication improvement of symptoms

6.21 The results of the FULFIL trial indicate that treatment with Trelegy may be associated with improvements in lung function (MCID 100-140 mL) and exacerbations (no MCID, large reduction) compared to ICS/LABA FDC but appeared to have a limited impact on functional symptoms (MCID, 4 points) and rescue medication use (no MCID, small reduction).

6.22 Similar to the IMPACT trial, patients in the FULFIL trial were required to be on prior maintenance therapy (inhaled monotherapy, dual therapy or triple therapy with or without theophylline) which was discontinued on the day before receiving trial treatments. The submission claimed that this approach is reflective of clinical practice rather than having an artificial washout/run-in periods used in many COPD trials. However, the absence of ICS/LABA or LAMA/LABA as a uniform treatment option during run-in period limits the ability to assess the efficacy of Trelegy as a step-up treatment option, as results may be confounded by other changes (such as the cessation of previous LAMA treatment in the comparator arm).

6.23 Additional pre-specified and post-hoc subgroup analyses of the FULFIL trial results suggest that baseline FEV_1, exacerbation history and prior therapies may affect comparative efficacy estimates.

6.24 The results from the FULFIL trial appeared to be substantially more favourable than top-line results from the IMPACT trial for the comparison of Trelegy versus ICS/LABA FDC (mean difference in the change in trough FEV_1 at 52 weeks: 179 mL vs. 97 mL; reduction in exacerbations at 52 weeks: RR 0.56 vs. 0.85). The reason for this apparent difference was unclear.

Comparative harms

6.25 No formal quantitative analysis was undertaken to evaluate the relative safety of fluticasone furoate, vilanterol and umeclidinium triple therapy with other comparator regimens on the basis that all individual components are already available on the PBS and that noninferiority has already been established between them. This approach was not reasonable. The draft Post-market Review of COPD medicines report noted that both meta-analyses and observational studies have reported an increased risk of pneumonia with prolonged ICS use. As such, it is reasonable to assume that triple therapy with Trelegy is likely to be associated with increased adverse events compared to dual therapy with LAMA/LABA FDCs. The DUSC agreed that there are ongoing safety concerns around the prolonged and unnecessary use of ICS in patients with COPD, and considered that given the potential for rapid escalation to triple therapy resulting from the availability of Trelegy and the disinclination of prescribers to remove ICS treatment if no clinical benefit is observed, this may further increase the risk of prolonged ICS use and related harms.

6.26 Based on the FULFIL trial, treatment with Trelegy was associated with an increased risk of infection (including pneumonia) compared to ICS/LABA. Subgroup analyses indicated that the risk of adverse events associated with Trelegy tended to increase with age. Results from longer-term FULFIL extension population generally demonstrated a similar overall incidence of adverse events with Trelegy compared to ICS/LABA.

6.27 Based on an expanded assessment of harms, important potential risks include hypersensitivity, serious cardiovascular events, adrenal suppression, corticosteroid associated eye disorders, narrow angle glaucoma, bladder outlet obstruction, dysuria and urinary retention, paradoxical bronchospasm and off-label use in asthma (including paediatric use). The submission also acknowledged that pneumonia is an important confirmed risk of ICS use in COPD populations.

Benefits and harms

6.28 The benefits and harms of any triple therapy combination of fluticasone furoate 100 mcg, umeclidinium 62.5 mcg and vilanterol 25 mcg (Trelegy or combination of fluticasone furoate/vilanterol FDC plus umeclidinium) versus fluticasone propionate 500 mcg/salmeterol 50 mcg FDC plus tiotropium 18 mcg were not presented given the claim of noninferiority in terms of efficacy and safety.

6.29 On the basis of available comparative data, the comparison of any triple therapy combination of LAMA, LABA and ICS versus any LAMA/LABA in patients with COPD resulted in:

- Limited to no difference in functional symptom scores and rescue medication use between treatments.
- Some improvement in lung function although the magnitude of benefit varied between comparisons over 52 weeks (approximately 16 to 117 mL change in trough FEV_1). It was unclear if this was a clinically meaningful difference given the nominated minimal clinically important difference of 100-140 mL change in FEV_1.
- Approximately 22-32% reduction in the rate of exacerbations over 52 weeks although the results were not always statistically significant between comparisons.
- An unknown difference in adverse events as no formal comparisons were provided.

6.30 On the basis of available comparative data, the comparison of any triple therapy combination of fluticasone furoate 100 mcg/umeclidinium 62.5 mcg/vilanterol 25 mcg (Trelegy or combination of fluticasone furoate/vilanterol FDC plus umeclidinium) and any ICS/LABA FDC in patients with COPD resulted in:

- Limited to no difference in functional symptom scores and rescue medication use between treatments.
- Some improvement in lung function although the magnitude of benefit varied between comparisons over 52 weeks (approximately 97 or 179 mL change in trough FEV_1). It was unclear if this was a clinically meaningful difference given the nominated minimal clinically important difference of 100-140 mL change in FEV_1.
- Some improvement in exacerbations although the magnitude of benefit varied between comparisons over 52 weeks (approximately 15 or 45% reduction in the rate of exacerbations).
- A potential increased risk of infection of uncertain magnitude.

Interpretation of clinical evidence

6.31 The submission described Trelegy as non-inferior in terms of efficacy and safety compared to fluticasone propionate/salmeterol FDC plus tiotropium (as a proxy for other triple therapies). This claim appeared plausible but was not strongly supported by the indirect clinical evidence presented in the submission.

6.32 The submission described Trelegy as superior in terms of efficacy and noninferior in terms of safety compared to dual LAMA/LABA therapy. The efficacy claim may be reasonable although the magnitude of benefit was unclear. The safety claim was not well supported by the clinical evidence presented in the submission and appears implausible. The final results of the IMPACT trial are likely to be informative to this clinical claim, although these were unable to be verified at the time of PBAC's consideration.

6.33 The PBAC considered that the claim of noninferior efficacy and safety compared to other triple therapy combinations of LAMA, LABA and ICS was reasonable.

6.34 The PBAC considered that the claim of superior comparative effectiveness over LAMA/LABA dual therapy may be reasonable, but that the magnitude of benefit was small and uncertain.

6.35 The PBAC considered that the claim of noninferior comparative safety compared to LAMA/LABA dual therapy was not adequately supported by the data, and that triple therapy was likely to have inferior safety compared to LAMA/LABA dual therapy.

Economic analysis

6.36 The submission presented a cost-minimisation analysis comparing Trelegy to fluticasone propionate 500 mcg/salmeterol 50 mcg FDC plus tiotropium 18 mcg, based on a clinical claim of noninferiority. In addition, the submission presented a cost-consequence analysis based on the incremental benefit of Trelegy over a LAMA/LABA FDC.

6.37 The equi-effective doses were estimated as:

- fluticasone furoate 100 mcg/umeclidinium 62.5 mcg/vilanterol 25 mcg FDC (1 inhalation once daily); and
- fluticasone propionate 500 mcg/salmeterol 50 mcg FDC (Seretide; 1 inhalation twice daily) plus tiotropium 18 mcg (1 inhalation once daily).

6.38 The estimated equi-effective doses were consistent with previous PBAC decisions and published therapeutic relativities in COPD.

6.39 The submission requested that the price of Trelegy be the same as the overall cost of fluticasone propionate 500 mcg/salmeterol 50 mcg FDC twice daily, plus tiotropium 18 mcg once daily, as a proxy for all triple therapy combinations. This approach may not be reasonable as triple therapy for COPD has not previously demonstrated cost effectiveness. The PSCR (p4) maintained that the approach taken in the cost-minimisation analysis is appropriate based on the clinical claim. The ESC considered

that the results from IMPACT could be used to conduct a cost utility analysis to determine the cost effectiveness of triple therapy.

6.40 As fluticasone propionate/salmeterol FDCs are listed on the PBS with a weighted price across listings for asthma and COPD, the COPD component price was used in the analysis. Drug costs were based on the 1 July 2016 Schedule, over 30 days of treatment. Results were updated for the 1 October 2017 Schedule during the evaluation.

Table 8: Price of Trelegy based on cost-minimisation analysis versus fluticasone propionate/salmeterol FDC plus tiotropium

Components	Max Qty	AEMP	DPMQ
Fluticasone propionate 500 mcg/salmeterol 50 mcg FDC (Seretide Accuhaler; 60 doses); plus	1	$[redacted]*	$[redacted]*
Tiotropium 18 mcg (Spiriva)	1	$44.95	$58.89
Trelegy (fluticasone furoate 100 mcg/vilanterol 25 mcg/umeclidinium 62.5 mcg FDC (30 doses)	1	$[redacted]	$[redacted]‡
Corrected using additive AEMP and updated to the 1 October 2017 Schedule		**$[redacted]†**	**$[redacted]**

Abbreviations: AEMP, approved ex-manufacturer price, DPMQ, dispensed price maximum quantity; FDC, fixed dose combination
Source: Table 106 (p 249) of the submission. Results in italics calculated during the evaluation
* Seretide AEMP and DPMQ adjusted for COPD component of the asthma/COPD weighted price, including a 1 June 2017 16% statutory price reduction
† Additive AEMP calculated during the evaluation; i.e. $[redacted] + $44.95 = $[redacted] AEMP
‡ Calculated for the submission by addition of DPMQs of concomitant therapies; i.e. $[redacted] + $58.89 = $[redacted] DPMQ

6.41 The cost-minimisation analysis estimated the price of Trelegy at $[redacted] (DPMQ), consistent with the claim for the same overall cost of therapy with the main comparator. Calculating the price of Trelegy at the AEMP level is preferred to the DPMQ level, and would result in a lower resultant dispensed price of $[redacted].

6.42 In addition, a cost-consequence analysis was presented, using methodology considered by the PBAC at its March 2014 meeting (Umeclidinium/vilanterol FDC Public Summary Document, March 2014), in which the incremental value of a LAMA/LABA FDC versus LAMA monotherapy was estimated at $[redacted] for each 1 mL improvement in trough FEV_1. In the current submission, the value of the incremental benefit of adding an ICS to an LAMA/LABA FDC (55 mL trough FEV_1 at 12 weeks based on an indirect comparison; Table 5), was estimated at $[redacted] (i.e. 55 × $[redacted]). This approach estimated the price of Trelegy at $[redacted] DPMQ (i.e. the DPMQ of the lowest priced LAMA/LABA of $89.48 + $[redacted]).

6.43 The Pre-PBAC response (p2) presented a revised cost-consequence analysis using efficacy data from the IMPACT trial. The improvement in trough FEV_1 at 52 weeks of Trelegy compared to LAMA/LABA reported in the IMPACT trial was 54 mL (95% CI 39 mL, 69 mL). Using the lower bound of the confidence interval to calculate an incremental price using the above method (39 mL x $[redacted]) resulted in a revised price advantage of $[redacted] over the price of LAMA/LABA. The sponsor offered a further discount, resulting in a price advantage of $[redacted] for Trelegy over the price of LAMA/LABA. The calculations in the Pre-PBAC response resulted in a revised offer of a dispensed price of $[redacted].

6.44 The cost-consequence analysis was insufficient to address the incremental difference in costs and outcomes (lung impairment, exacerbations, functional symptoms, quality

of life, safety) between treatments. The magnitude of benefit of change from baseline in trough FEV_1 reported in the indirect comparison was highly uncertain, and while the difference was statistically significant, it was less than the minimum clinically important difference used in the submission (MCID 100-140 mL). The ESC noted that, in the absence of a reliable estimate of an incremental benefit of triple therapy over dual therapy, it may be more appropriate for the price of Trelegy to more closely align with the price of LAMA/LABA dual therapy.

6.45 Under Section 101(3B) of the *National Health Act 1953*, where a therapy is substantially more costly than an alternative therapy or alternative therapies, the PBAC shall not recommend to the Minister that the drug be made available as a pharmaceutical benefit unless the Committee is satisfied that the therapy, for some patients, provides a significant improvement in efficacy or reduction in toxicity over alternative therapies. The requested price of Trelegy is more costly than the alternative therapy, LAMA/LABA.

Drug cost/patient/year: $[redacted]

6.46 The cost of treating one patient over 12 months with Trelegy FDC was [redacted] (calculated as the initially requested DPMQ of $[redacted]×365.25/30 doses). Using the price of Trelegy derived from adding the AEMPs of the comparator products (DPMQ of $[redacted]), the cost per patient per year would be $[redacted]

Estimated PBS usage & financial implications

6.47 This submission was considered by DUSC.

6.48 The submission used a market share approach to estimate the utilisation and financial impacts associated with the PBS listing of Trelegy.

6.49 The financial estimates assumed that a proportion of patients treated with triple therapy with ICS/LABA FDC plus LAMA will switch to Trelegy. Eligible patients using other triple therapy combinations (e.g. LAMA/LABA FDC plus ICS) were inappropriately excluded from the analysis.

6.50 The submission argued that PBS listing of Trelegy was not expected to result in any significant growth of the overall COPD market. However, there is potential for additional market growth due to:

- patients who would otherwise have been adequately managed with mono or dual therapy switching to Trelegy (due to the convenience of the Trelegy dosing regimen, and no additional co-payment for Trelegy compared to mono or dual therapy);
- positive headline results from the IMPACT trial which may lead to triple therapy market growth through increased prescribing of Trelegy;
- possible improved treatment adherence with Trelegy;
- use of Trelegy outside of the PBS restriction in patients with asthma, or in patients with less severe forms of COPD.

6.51 The key source of data used to inform the financial estimates was a 10% Medicare sample. The submission defined a COPD patient cohort comprised of patients dispensed a LAMA, LAMA/LABA FDC, or LAMA monotherapy between January 2005 and December 2016, and applied treatment coverage rules to estimate the proportion of COPD patients treated with ICS/LABA FDC plus LAMA triple therapy. The use of a 6-month period between dispensed scripts to determine breaks in therapy may overestimate co-administration of COPD therapies and underestimate treatment switching and discontinuations. The COPD cohort included patients with less severe COPD who may not be eligible for Trelegy.

6.52 The derived patient proportions were applied to COPD cohort script volume data for ICS/LABA FDC plus LAMA component medicines to obtain monthly prescription counts. It was unclear whether the triple therapy utilisation estimates derived through application of the patient proportions to script volumes were reliable.

6.53 The submission extrapolated estimated 2016 prescription volumes for each of the triple therapy component medicines by applying a negative growth rate of [redacted]% per year. The growth rate used in the financial estimates was not adequately justified, and is unlikely to reflect the growth of the individual medicines considered in the analysis.

6.54 Table 9 presents the estimated utilisation and financial impact of Trelegy over the first six years of listing. The DUSC considered that the lack of detail provided around the methodology used to estimate PBS usage and financial implications provided in the submission made validation of the estimates challenging, but that overall the estimates presented in the submission were likely underestimated.

Table 9: Estimation of use and financial impact of Trelegy

	Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)	Year 6 (2023)
Estimated Trelegy scripts						
COPD market growth rate	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Estimated ICS/LABA triple therapy scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated LAMA triple therapy scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Correction factor applied to LAMA triple therapy scripts (88%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated market share	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Equivalent Trelegy scripts (one Trelegy script per ICS/LABA + LAMA)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trelegy PBS cost	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Trelegy co-payments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Trelegy cost less co-payments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated displaced scripts						
Displaced ICS/LABA triple therapy scripts[1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Displaced LAMA triple therapy scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Triple therapy PBS cost	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Triple therapy co-payments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Triple therapy cost less co-payments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net changes to the PBS/RPBS						
Net cost to PBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net co-payments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS (less co-payments)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Abbreviations: COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long acting beta agonist; LAMA, long acting muscarinic antagonist.
Source: Table 110 (p 258-259), Table 111 (p 260-261), Table 112 (p 262-263) of the submission.
[1] Lower numbers of ICS/LABA scripts compared to LAMA scripts due to provision of two months supply of Symbicort 400/12 Turbuhaler and Symbicort 200/6 Rapihaler per dispensing.

6.55 The submission estimated a total net cost of less than $10 million over the first six years of listing. The increased cost to the PBS was primarily due to a reduction in the number co-payments received for Trelegy compared to the component ICS/LABA FDC plus LAMA triple therapy regimens.

6.56 There is potential for the cost to government to be higher than forecast due to the exclusion of alternative triple therapy combinations from the analysis, higher than estimated market share for Trelegy, growth of the triple therapy market following PBS listing of Trelegy, and inappropriate use in the treatment of asthma.

6.57 The DUSC considered that whilst there may be reductions in hospital admissions if COPD exacerbations are reduced, the increased risk of pneumonia from ICS may contribute to higher rates of hospital admissions for treatment. As such, any change in hospitalisation is likely unable to be quantified from the information available.

6.58 The Pre-PBAC response (p4) updated the financial estimates based on the revised price offer (DPMQ $[redacted]) and [redacted]% or [redacted]% market share, resulting in cost savings to the R/PBS over 6 years of less than $10 million.

Quality use of medicines

6.59 The submission identified medication errors, potential for off-label use, and proliferation of COPD medicines as the main quality use of medicines issues.

6.60 The submission acknowledged that some patients may inappropriately administer Trelegy multiple times a day, but argued that the risk was low given once daily dosing was a key feature of Trelegy. There may be potential for adverse events resulting from duplication of therapy due to inappropriate use of Trelegy in combination with other COPD medicines.

6.61 The submission acknowledged the potential for Trelegy to be used outside of the PBS restriction for the treatment of asthma or less severe forms of COPD.

6.62 The submission claimed that PBS listing of Trelegy would address an unmet clinical need for a single triple therapy inhaler, and would not represent unnecessary proliferation of products or dose forms. The DUSC noted that PBS-listing of Trelegy would mean that a product in an Ellipta device would be available at all stages of the COPD-X stepwise management plan (mild, moderate and severe disease). While this may contribute to the correct use of the device, it may also facilitate more rapid escalation to triple therapy, which may not be warranted.

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

Financial management – risk sharing arrangements

6.63 No risk sharing arrangement was proposed in the submission.

6.64 The PBAC considered that due to concerns raised by DUSC about underestimated market share and market growth, as well as quality use of medicines issues identified in relation to use earlier in the treatment pathway than clinically appropriate, a risk sharing arrangement was appropriate.

6.65 The PBAC considered that a risk sharing arrangement based on estimated utilisation with [redacted]% market share, as proposed in Scenario 2 of the Pre-PBAC response (p4), was appropriate. Should any price advantage for Trelegy over the price of dual therapy be agreed to, the PBAC considered that a cap based on the submission's estimates should be in place, with the price of Trelegy reducing to the price of LAMA/LABA dual therapy if the cap is exceeded.

7 PBAC outcome

7.1 The PBAC recommended an Authority Required (Streamlined) listing of fluticasone furoate with umeclidinium and vilanterol (Trelegy) for the treatment of chronic obstructive pulmonary disease (COPD). Noting that triple therapy for COPD has not previously been assessed as being cost-effective, the PBAC advised that Trelegy could be acceptably cost-effective if a small price advantage was negotiated over the price

of currently listed LAMA/LABA FDCs, such as umeclidinium 62.5 mcg/vilanterol 25 mcg FDC, 1 inhalation once daily.

7.2 The PBAC was concerned that an Authority Required (Streamlined) listing may not adequately limit use of the product to the most severe patients who require treatment with triple therapy. However, noting that it is possible to prescribe triple therapy via concomitant use of its components through existing restrictions, the PBAC considered that the proposed restriction level for Trelegy appeared appropriate at this time.

7.3 The PBAC considered that LAMA/LABA dual therapy, and triple therapy via concomitant use of any combination of LAMA, LABA and ICS were appropriate comparators.

7.4 The PBAC accepted that, based on the indirect evidence provided, Trelegy is likely to be non-inferior in terms of safety and efficacy compared to concomitant use of LAMA, LABA and ICS, and that whilst this was informative, this was not the appropriate main comparison for determining the cost effectiveness of Trelegy.

7.5 The PBAC considered that, on the basis of the indirect comparison presented in the submission, triple therapy with Trelegy might be associated with a modest improvement in efficacy in terms of lung function and exacerbations over dual therapy with LAMA/LABA. However, the PBAC noted that the unevaluated results from the IMPACT trial indicated the magnitude of this improvement was smaller than presented in the indirect comparison, and as such it was difficult to reliably quantify the incremental benefit of triple therapy over dual therapy.

7.6 Noting the findings of the Post-market Review of COPD medicines, the PBAC considered that triple therapy with Trelegy was also likely to be associated with an increased risk of harms over dual therapy with LAMA/LABA, particularly in relation to pneumonia. As such, the PBAC considered that the appropriate place in therapy for Trelegy should be following inadequate control with dual therapy. The PBAC hence recommended that the listing for Trelegy should specify that patients must have a history of repeated exacerbations with significant symptoms despite regular therapy with a long acting muscarinic antagonist (LAMA) and a long acting beta-2 agonist (LABA) or an inhaled corticosteroid (ICS) and a LABA. The PBAC recommended that the restriction should alternatively provide for patients who are stabilised on a combination of a LAMA, a LABA and an ICS to switch to Trelegy.

7.7 The PBAC therefore considered that, based on the assessment of benefits and harms of triple therapy with Trelegy over LAMA/LABA dual therapy, any improvement in efficacy should be balanced against the increased harms from prolonged ICS exposure in COPD patients. Under Section 101(3B) of the *National Health Act 1953,* the PBAC was satisfied that, for some patients, there was a significant improvement in efficacy sufficient to justify that triple therapy with Trelegy could be more costly than the alternative therapy, LAMA/LABA. As such, the PBAC advised that a small price advantage could be negotiated for Trelegy over the price of a currently listed LAMA/LABA FDC to reflect this likely small improvement in efficacy and unquantified increase in toxicity.

7.8 The PBAC noted that the IMPACT trial could be used to inform a cost-effectiveness analysis of triple therapy in COPD over dual therapy with LAMA/LABA in order to more reliably determine the magnitude of any incremental benefit and give a better estimate of the cost-effectiveness of triple therapy. Any formal cost-effectiveness analysis presented should also consider increased costs associated with managing more adverse events associated with ICS exposure. Also, if a cost-effectiveness analysis was presented, the ceiling price of Trelegy (or any other fixed combination of triple therapy of LAMA/LABA/ICS) should be no greater than the lowest priced combination of any listed components of the triple therapy, with the price of the fixed combination triple therapy calculated by adding the AEMPs of these components to calculate the AEMP of the fixed combination and thus its DPMQ.

7.9 The PBAC considered that the estimated use and financial implications were highly uncertain and underestimated, and that due to growth in the triple therapy market, the total cost to the PBS was likely to increase even in light of the price reduction offered in the Pre-PBAC response.

7.10 The PBAC recommended DUSC review the use of Trelegy two years after listing. The PBAC advised that it will consider increasing the authority level to telephone authority if triple therapy market growth has been inappropriate.

7.11 The PBAC recommended that fluticasone furoate with umeclidinium and vilanterol should not be treated as interchangeable on an individual patient basis with any other drugs.

7.12 The PBAC advised that fluticasone furoate with umeclidinium and vilanterol is suitable for prescribing by nurse practitioners for continuing treatment only.

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

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 item

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
FLUTICASONE FUROATE + UMECLIDINIUM + VILANTEROL Fluticasone furoate 100 microgram/actuation + umeclidinium 62.5 microgram/actuation + vilanterol 25 microgram/actuation	1	5	Trelegy® Ellipta®	GSK

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☒ Nurse practitioners ☐ Optometrists ☐ Midwives
Episodicity:	-
Severity:	-
Condition:	Chronic Obstructive Pulmonary Disease
PBS Indication:	Chronic Obstructive Pulmonary Disease
Treatment phase:	-
Restriction Level / Method:	☐ Restricted benefit ☐ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required - Emergency ☐ Authority Required - Electronic ☒ Streamlined
Treatment criteria:	-
Clinical criteria:	Patient must have a forced expiratory volume in 1 second (FEV_1) less than 50% of predicted normal prior to therapy AND Patient must have a history of repeated exacerbations with significant symptoms despite regular long-acting 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, a LABA and an ICS for this condition.*
Population criteria:	-
Foreword	-
Definitions	-
Prescriber Instructions	-

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. Diagnosis of COPD should be confirmed with spirometry. This product is not PBS-subsidised for the treatment of asthma. This product is not indicated for the initiation of bronchodilator therapy in COPD. The treatment must not be used in combination with an ICS/LABA, LABA/LAMA or LAMA, LABA or ICS monotherapy. A LAMA includes tiotropium, glycopyrronium, aclidinium or umeclidinium. A LABA includes olodaterol, indacaterol, salmeterol, eformoterol or vilanterol. An ICS includes fluticasone propionate, fluticasone furoate, budesonide, beclomethasone or ciclesonide. Continuing therapy only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of a medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.
Cautions	-

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

GSK welcomes the PBAC recommendation to list Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol) on the PBS for the treatment of COPD. Trelegy Ellipta is the first single inhaler triple therapy for the treatment of COPD.