

## **6.08 FLUTICASONE FUROATE with UMECLIDINIUM and VILANTEROL,**

**Powder for oral inhalation in breath actuated device containing fluticasone furoate 100 micrograms with umeclidinium 62.5 micrograms (as bromide) and vilanterol 25 microgram (as trifenate) per dose, 30 actuations,**

**Trelegy® Ellipta®, GlaxoSmithKline.**

### **1 Purpose of Application**

- 1.1 The submission requested an extension to the current PBS listing of Trelegy® Ellipta® (referred to as Trelegy herein), the fixed dose combination (FDC) of fluticasone furoate (FF) 100mcg, an inhaled corticosteroid (ICS) with umeclidinium (UMEC) 62.5mcg, a long acting muscarinic receptor antagonist (LAMA) and vilanterol (VI) 25mcg, a long acting beta-2 adrenoreceptor agonist (LABA), for treatment of patients with chronic obstructive pulmonary disease (COPD), specifically the removal of the clinical criteria restricting access to patients with a forced expiratory volume in one second (FEV1) <50% of predicted. The PBAC has not previously considered use of Trelegy in the requested population (i.e. in patients with FEV1 ≥50% predicted).
- 1.2 The basis for the extended restriction was acceptable cost-effectiveness versus dual therapy LAMA/ LABA, informed by the combination of UMEC 62.5mcg and VI 25mcg. Given acceptable cost-effectiveness in patients with FEV1 ≥50% predicted, the submission formally requested removal of subsidisation caps in the current risk-sharing agreement.

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

Component	Description
Population	Patients with moderate to severe COPD and frequent exacerbations (with significant symptoms despite maintenance therapy of LAMA/LABA or ICS/LABA).
Intervention	Trelegy inhaled once daily, a triple therapy ICS/LAMA/LABA FDC, comprising of FF/UMEC/VI 100mcg/62.5mcg/25mcg.
Comparator	Dual therapy comprising LAMA/LABA inhaled once daily, informed by UMEC/VI 62.5mcg/25mcg.
Outcomes	Annual rate of moderate or severe exacerbations of COPD Time to first on-treatment moderate or severe exacerbations of COPD LS mean change from baseline in trough FEV1 Health related quality of life (SGRQ total score) Annual rate of on-treatment severe exacerbations of COPD Time to on-treatment all-cause mortality
Clinical claim	In COPD patients with moderate to severe disease who are at risk of exacerbations despite maintenance therapy, Trelegy compared with dual therapy comprising LABA/LAMA is more effective at reducing the risk of exacerbations and improving lung function; and comparable in terms of safety.

Abbreviations: COPD=chronic obstructive pulmonary disease; FEV1=forced expiratory volume in one second; FF=fluticasone furoate; ICS=inhaled corticosteroid; LABA=long acting beta-2 agonist; LAMA=long acting muscarinic antagonist; LS=least squares; mcg=microgram; SGRQ=St George's Respiratory Questionnaire; UMEC=umeclidinium; VI=vilanterol;  
Source: Table 1, p15 of the submission.

## 2 Requested listing

2.1 Amendments to the current PBS listing of Trelegy for the treatment of COPD proposed by the submission are shown in bold with strikethrough used for deletions and additions underlined. Suggestions proposed by the Secretariat to the requested listing are shaded in grey with strikethrough used for deletions and additions in italics.

Name, Restriction, Manner of administration and form	Max. Qty (packs)	Max Qty (units)	No. 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 powder for inhalation, 30 ACTUATIONS	1	1	5	\$97.35	Trelegy® Ellipta® GSK

<b>Category / Program:</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse Practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>PBS Indication:</b>	Chronic Obstructive Pulmonary Disease ( <i>COPD</i> )

Public Summary Document – March 2019 PBAC Meeting

<b>Category / Program:</b>	GENERAL – General Schedule (Code GE)
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p><del>Patient must have a forced expiratory volume in 1 second (FEV<sub>1</sub>) less than 50% of predicted normal prior to therapy AND</del></p> <p>Patient must have a history of repeated experienced at least one severe COPD exacerbations, which required hospitalisation, or two or more moderate exacerbations in the previous 12 months, 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</p> <p>Patient must have been stabilised on a combination of a LAMA, a LABA and an ICS for this condition.</p>
<b>Administrative Advice:</b>	<p>Formal assessment and correction of inhaler technique should be performed in accordance with the COPD-X Plan (available at <a href="http://copdx.org.au/">http://copdx.org.au/</a>); the assessment and adherence to correct technique should be documented in the patient's medical records.</p> <p><del>Diagnosis of COPD should be confirmed with spirometry. Spirometry is required to confirm diagnosis of COPD and should be considered as a method for monitoring disease progression and assessing treatment response.</del></p> <p>This product is not PBS-subsidised for the treatment of asthma <i>or the</i>  <del>This product is not indicated for the</del> 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.</p> <p>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.</p> <p>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.</p>

Abbreviations: COPD=chronic obstructive pulmonary disease; FEV<sub>1</sub>=forced expiratory volume in one second; FF=fluticasone furoate; ICS=inhaled corticosteroid; LABA=long-acting beta-2 agonist; LAMA=long-acting muscarinic antagonist; UMEC=umeclidinium; VI=vilanterol;

Source: Table 8, pp28-29 of the submission.

2.2 The submission requested the removal of the clinical criteria “Patient must have a forced expiratory volume in 1 second (FEV<sub>1</sub>) less than 50% of predicted normal prior

to therapy” and wording added to administrative advice emphasising the importance of spirometry testing. All other aspects of the requested restriction (Section 85, Authority Required STREAMLINED, quantity, repeats and price) remain unchanged from the current PBS listing of Trelegy for treatment of patients with COPD.

- 2.3 The request to remove the FEV1 threshold from the clinical criteria in the PBS restriction for Trelegy is consistent with the update to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (2017-18). However, while GOLD guidelines refer to moderate to severe exacerbation history in the prior year, the PBS restriction does not specify exacerbation severity and also does not specify that exacerbation history as occurring within the previous 12 months. The PBAC also noted that the proposed removal of the FEV1 threshold was not consistent with the current COPD-X (December, 2018) Guidelines which could cause prescriber confusion.
- 2.4 The ESC agreed with the Secretariat’s proposed changes to the restriction with respect to specification of exacerbation severity and the 12 month time period for the exacerbation history. The ESC considered that, in accordance with GOLD guidelines, it may also be appropriate for either the COPD Assessment Test (CAT) or the Modified British Medical Research Council questionnaire score (mMRC) to be incorporated in the proposed restriction. The pre-PBAC response argued that the CAT score should not be included in the restriction as it is not routinely used in clinical practice and is not included in PBS restrictions for other COPD medicines. The PBAC did not consider the incorporation of the CAT or the mMRC score in the restriction would be appropriate as clinicians would not be familiar with it. The PBAC instead advised that the restriction continue to make reference to the need for a patient to be experiencing significant symptoms despite LAMA/LABA therapy. The PBAC also considered that the restriction should include reference to the importance of spirometry in the diagnosis of COPD with the administrative advice consistent with current LAMA/LABA and ICS/LABA FDC restrictions in relation to this issue. The PBAC considered that, with these changes made to the restriction, it would be appropriate to remove the FEV1 criterion. However, even with the proposed changes to the restriction the PBAC remained concerned regarding the potential use of Trelegy earlier in the treatment algorithm than clinically appropriate.
- 2.5 The submission also stated (p 28) that as current PBS listings for ICS/LABA combination products also contain this historical spirometric requirement, the requested amendment in this submission is also considered applicable to all PBS listed ICS/LABA products. It is noted that the TGA indications for ICS/LABA FDCs currently restrict use to patients with FEV1<50% or <70% predicted (depending on the product). The PBAC considered that it would be appropriate for the request to remove the FEV1 threshold from the Trelegy clinical criteria to be applied to the COPD indication for all ICS/LABA FDC products to maintain consistency. However, the PBAC advised that that any such change to the ICS/LABA FDC restriction should also be accompanied by specification

of the exacerbation severity and the 12 month time period for the exacerbation history.

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

### **3 Background**

#### ***Current PBS listing***

- 3.1 The PBAC recommended the listing of Trelegy in December 2017 for treatment of COPD in patients with FEV1 <50% predicted and history of repeated exacerbations with significant symptoms despite maintenance with dual therapy LAMA and LABA, or an ICS.
- 3.2 The requested listing in the December 2017 submission was on the basis of cost-minimisation to triple therapy with fluticasone propionate 500 mcg/salmeterol 50 mcg FDC twice daily plus tiotropium 18 mcg once daily as proxy for all ICS, LABA and LAMA combinations. The previous submission also presented a cost-consequence analysis of Trelegy versus any LAMA/LABA FDC. On the grounds of the indirect evidence presented, the PBAC accepted that Trelegy is likely to be non-inferior in terms of efficacy and safety compared to concomitant use of LAMA, LABA and ICS, and “whilst this was informative, this was not the appropriate main comparison for determining cost effectiveness of Trelegy” (Paragraph 7.4, Trelegy Public Summary Document (PSD), December 2017).
- 3.3 The PBAC considered “Trelegy might be associated with a modest improvement in efficacy in terms of lung function and exacerbations over dual therapy with LAMA/LABA” based on indirect evidence, and recommended a “small price advantage ... over the price of a currently listed LAMA/LABA FDC” (Paragraphs 7.5 and 7.7, Trelegy PSD, December 2017).
- 3.4 Although limited data from the IMPACT trial was available at that time, the PBAC considered “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” (Paragraph 7.8, Trelegy PSD, December 2017). The PBAC noted that this was not the purpose of the current submission. Instead, the current submission presented a cost utility analysis based on the results of the IMPACT trial to justify the removal of the FEV1 threshold in the current restriction and the removal of the current Risk Sharing Arrangement and subsidisation caps.
- 3.5 The previous Trelegy submission was reviewed by DUSC. DUSC noted that the 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 practice and the accuracy of tests in determining disease

severity. DUSC considered that there was a high risk that Trelegy will be used outside of the PBS restriction earlier in the treatment pathway than may be clinically appropriate, in less severe disease, and in asthma. This was likely to grow the triple therapy market as patients who would otherwise be managed with mono- or dual therapy may initiate triple therapy. The ESC considered that the risk of use outside of restriction and concerns raised regarding the inappropriate escalation to triple therapy remain relevant to the current submission.

### **Registration status**

- 3.6 Trelegy was TGA registered on the 16 January 2018 for “the maintenance treatment of adults with moderate to severe COPD who require treatment with LAMA+LABA+ ICS. Trelegy Ellipta is not indicated for the initiation of therapy in COPD.” The Sponsor submitted a category 1 application to the TGA on the 25th May 2018 to include data from the IMPACT trial in the product information (PI).
- 3.7 The requested listing was generally consistent with the TGA indication despite no universal grading for COPD severity. While the Australian COPD-X guidelines define ‘moderate to severe’ disease based on symptoms and airflow obstruction (FEV1 % predicted < “≈59%”), GOLD treatment guidelines separately classify severity for airflow obstruction (mild to very severe, based on FEV1 % predicted), exacerbations (mild to severe based on required treatment and hospitalisation), and symptoms (‘less’ or ‘more’ based on self-assessed questionnaires).

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

## **4 Population and disease**

- 4.1 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, exposure to noxious particles or gases (most commonly cigarette smoke) can result in exacerbations, hospitalisations and death.
- 4.2 The severity of airflow limitation in COPD is measured using spirometry and defined based on FEV1 % predicted. However, there is only a weak correlation between FEV1 % predicted, symptoms and impairment of a patient’s health status. The ESC considered that, while FEV1 is a good marker of disease severity, it is not a good determinant of a patient’s future risk of exacerbations.
- 4.3 Prior to 2017, GOLD treatment guidelines recommended pharmacotherapy using spirometry criteria based on early evidence that patients with ‘severe’ lung function impairment (FEV1 <50% predicted) were prone to repeated exacerbations and hospitalisation. However, updated guidelines reflect current evidence indicating that

history of previous exacerbations is the best predictor of future episodes and patients with FEV1  $\geq$ 50% predicted can experience frequent exacerbations.

- 4.4 GOLD (2018) recommends stepwise pharmacotherapy based on exacerbation history and symptoms, irrespective of FEV1 % predicted. In particular, the guidelines recommend triple therapy ICS/LAMA/LABA as a step up for patients at high risk of exacerbations ( $\geq$ 2 moderate exacerbations or  $\geq$ 1 severe exacerbation in past 12 months) with significant symptoms (mMRC  $\geq$ 2, CAT  $\geq$ 10), after dual therapy (LAMA/LABA or ICS/LABA). The ESC noted GOLD's refined ABCD assessment tool which indicates that triple therapy be reserved for patients at highest risk of exacerbations, i.e. those in 'Group D'.
- 4.5 The ESC noted that the Australian COPD-X Guidelines still use FEV1 to classify COPD severity. The ESC noted that the submission stated that the COPD-X guidelines are 'written in consideration of the existing PBS criteria. Removal of the spirometric requirement in the PBS criteria would result in an amendment to the Guidelines.' While noting this comment in the submission, the PBAC felt that it was not substantiated or justified but did note that the COPD-X Guidelines are updated every 3 months. The PBAC noted the inconsistency between the GOLD and COPD-X guidelines in terms of the use of FEV1 criteria to classify COPD severity.

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

## **5 Comparator**

- 5.1 Dual therapy LAMA/LABA FDC, informed by the dry-powder inhaler Anoro<sup>®</sup> FDC (UMEC 62.5mcg / VI 25mcg) administered as one inhalation once daily. In December 2017, the PBAC considered that dual therapy LAMA/LABA was the appropriate comparator for determining the cost-effectiveness of triple therapy with 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 that no consumer comments were received for this item.

## Clinical trials

6.3 The submission was based on one head-to-head randomised trial (IMPACT) comparing Trelegy FDC (FF 100mcg / UMEC 62.5mcg / VI 25mcg) to Anoro FDC (UMEC 62.5mcg / VI 25mcg), summarised in the table below.

**Table 2: Trials presented in the submission**

Trial ID	Publication title	Publication citation
IMPACT	Clinical Study Report (CSR): A Phase III, 52 week, randomised, double blind, 3-arm parallel group study, comparing the efficacy, safety and tolerability of the fixed dose triple combination FF/UMEC/VI with the fixed dose dual combinations of FF/VI and UMEC/VI, all administered once-daily in the morning via a dry powder inhaler in subjects with chronic obstructive pulmonary disease.	CSR* IMPACT, 10 Jan 2018
	Lipson DA, Barnhart F, Brealey N et al 2018. Once-daily single-inhaler triple versus dual therapy in patients with COPD	The New England Journal of Medicine; 378:1671-1680.10.1056/NEJMoA1713901.

Abbreviations: COPD=chronic obstructive pulmonary disorder; FF=fluticasone fumarate; LABA=long acting beta agonist; LAMA=long acting muscarinic antagonist; UMEC=umeclidinium; VI=vilanterol;

\* CSR obtained from sponsor's database were the primary source for data extractions

Source: Table 12, p34 of the submission.

6.4 The key features of IMPACT are summarised in the table below.

**Table 3: Key features of IMPACT trial**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
IMPACT	10,355	MC, R, DB (52 weeks), 3-arm	Low	COPD with exacerbations on treatment	Annual rate of exacerbations, lung function (FEV1), all-cause mortality, quality of life	Annual rate of exacerbations, lung function (FEV1)

Abbreviations: COPD=chronic obstructive pulmonary disease; DB=double blind; FEV1=forced expiratory volume in one second; FF=fluticasone furoate; ICS=inhaled corticosteroid; LABA=long-acting beta-2 agonist; LAMA=long-acting muscarinic antagonist; MC=multi-centre; mcg=microgram; OL=open label; OS=overall survival; R=randomised; UMEC=umeclidinium; VI=vilanterol;

Source: Section 2.3, pp36-40 of the submission.

6.5 Eligible patients were required to demonstrate at screening:

- CAT score  $\geq 10$ ; and
- post-bronchodilator FEV1  $< 50\%$  predicted with a documented history of  $\geq 1$  moderate or severe exacerbations in past 12 months, or post-bronchodilator  $50\% \leq$  FEV1  $< 80\%$  predicted with a history of  $\geq 2$  moderate or  $\geq 1$  severe exacerbations (hospitalised) in the past 12 months.

6.6 The IMPACT trial investigated the efficacy and safety of Trelegy FDC (FF 100mcg / UMEC 62.5mcg / VI 25mcg) versus dual therapies Breo FDC (FF 100mcg / VI 25mcg) and Anoro FDC (UMEC 62.5mcg / VI 25mcg), in patients with symptomatic COPD taking

any regular long-acting bronchodilator therapy (for  $\geq 3$  months at screening). Patients were randomised 2:2:1 respectively.

- 6.7 The ESC noted that the submission primarily used evidence from IMPACT to establish the effectiveness of Trelegy in the broader population (i.e. currently eligible patients (FEV1 <50% predicted) as well as patients who will become eligible under the requested extension to the PBS listing (FEV1  $\geq 50\%$  predicted)). However, the submission acknowledged that the trial population in IMPACT was heterogeneous with respect to FEV1 % predicted, exacerbation history and prior therapy; and may not be wholly representative of the requested PBS population (defined as patients with a history of repeated exacerbations with significant symptoms despite treatment with dual LAMA/LABA or ICS/LABA). To address potential applicability concerns, the submission presented a series of *post hoc* subgroup analyses to examine whether baseline FEV1 % predicted and exacerbation history, or prior treatment were significant modifiers of treatment effect for key outcomes. The ESC considered that the *post hoc* analyses presented in the submission reduced concerns regarding translation of the IMPACT trial results to the requested PBS population.
- 6.8 The absence of a uniform run-in period of dual therapy potentially limits the applicability of the trial results to inform the efficacy of Trelegy as a step up treatment from a LAMA/LABA. Fewer than 10% of the trial population were taking a LAMA/LABA at baseline, and hence stepped-up to ICS/LAMA/LABA. Nevertheless, the ESC considered that the *post-hoc* analysis presented in the submission suggested that the relative treatment effects by prior therapy were generally similar to the intention-to-treat (ITT) population.

### **Comparative effectiveness**

- 6.9 Table 4 summarises the key efficacy outcomes reported in IMPACT (ITT).

**Table 4: Key efficacy outcomes reported in the IMPACT trial**

Outcome	FF/UMEC/VI N=4151	FF/VI N=4134	UMEC/VI N=2070	Treatment difference (95% CI)	
				FF/UMEC/VI vs FF/VI	FF/UMEC/VI vs UMEC/VI
<b>Annual rate of on-treatment exacerbation</b>					
Total duration at risk (yrs)	3714.9	3457.9	1698.3	-	-
Total exacerbations	3428	3636	1949	-	-
Moderate (%)	2868 (83.7)	3054 (84.0)	1607 (82.5)	-	-
Severe (%)	560 (16.3)	582 (16.0)	342 (17.5)	-	-
Rate <sup>#</sup> of moderate / severe	0.92	1.05	1.15	-	-
Rate <sup>#</sup> of severe	0.15	0.17	0.20	-	-
GLM predicted rate <sup>a</sup> (95%CI)	n=4145	n=4133	n=2069	RR	RR
Moderate / severe	0.91 (0.87, 0.95)	1.07 (1.02, 1.12)	1.21 (1.14, 1.29)	<b>0.85 (0.80, 0.90)</b>	<b>0.75 (0.70, 0.81)</b>
Severe	0.13 (0.12, 0.14)	0.15 (0.13, 0.16)	0.19 (0.17, 0.22)	<b>0.87 (0.76, 1.01)</b>	<b>0.66 (0.56, 0.78)</b>
<b>Time to first on-treatment exacerbation</b>					
N with event (%)				HR <sup>b</sup>	HR <sup>b</sup>
Moderate / severe	1959 (47)	2039 (49)	1036 (50)	<b>0.85 (0.80, 0.91)</b>	<b>0.84 (0.78, 0.91)</b>
Severe	447 (11)	461 (11)	272 (13)	0.89 (0.78, 1.01)	<b>0.75 (0.64, 0.87)</b>
<b>Change from baseline in trough FEV1 (mL)</b>					
LS mean change <sup>c</sup>	n=3366	n=3060	n=1490		
At Wk52, (95%CI)	94 (86, 102)	-3 (-12, 6)	40 (28, 52)	<b>97 (85, 109)</b>	<b>54 (39, 69)</b>
<b>Proportion of FEV1 responders (with ≥100mL increase from baseline in trough FEV1)</b>					
Responders <sup>d</sup>	n=4138	n=4127	n=2068	OR <sup>e</sup>	OR <sup>e</sup>
At Wk52, n(%)	1561 (38)	939 (23)	561 (27)	<b>2.07 (1.88, 2.28)</b>	<b>1.64 (1.46, 1.84)</b>
<b>Time to all-cause mortality</b>					
N with event (%)				HR <sup>b</sup>	HR <sup>b</sup>
On-treatment	1.20%	1.19%	1.88%	0.95 (0.64, 1.40)	<b>0.58 (0.38, 0.88)</b>
On- and off-treatment	2.14%	2.35%	2.90%	0.90 (0.67, 1.20)	<b>0.71 (0.51, 0.99)</b>
<b>Change from baseline in SGRQ-C total score</b>					
LS mean change <sup>c</sup>	n=3318	n=3026	n=1470		
At Wk52, (95%CI)	-5.5 (-5.9, 5.0)	-3.7 (-4.2, -3.2)	-3.7 (-4.4, 3.0)	<b>-1.8 (-2.4, -1.1)</b>	<b>-1.8 (-2.6, -1.0)</b>
<b>Proportion of SGRQ-C responders (total score ≤4 units below baseline)</b>					
Responders <sup>d</sup>	n=4108	n=4092	n=2050	OR <sup>e</sup>	OR <sup>e</sup>
At Wk52, n(%)	1723 (42)	1390 (34)	696 (34)	1.41 (1.29, 1.55)	1.41 (1.26, 1.57)
<b>Change from Baseline CAT Score</b>					
LS mean change <sup>c</sup>	n=3270	n=2979	n=1451		
At Wk52, (95%CI)	-2.0 (-2.3, -1.8)	-1.5 (-1.7, -1.3)	-1.6 (-1.9, -1.3)	<b>-0.5 (-0.8, -0.2)</b>	<b>-0.4 (-0.8, -0.1)</b>

Outcome	FF/UMEC/VI N=4151	FF/VI N=4134	UMEC/VI N=2070	Treatment difference (95% CI)	
				FF/UMEC/VI vs FF/VI	FF/UMEC/VI vs UMEC/VI
<b>Proportion of CAT responders (CAT score <math>\leq 2</math> units below baseline)</b>					
Responders <sup>d</sup>	n=4076	n=4047	n=2034	OR <sup>e</sup>	OR <sup>e</sup>
At Wk52, n(%)	1698 (42)	1491 (37)	730 (36)	<b>1.24 (1.14, 1.36)</b>	<b>1.28 (1.15, 1.43)</b>

Abbreviations: CAT=COPD Assessment Test; CI=confidence interval; FEV1=forced expiratory volume in one second; FF=fluticasone fumarate; GLM=generalised linear model; HR=hazard ratio; ITT=intention to treat; LS=least square; n=number of patients with event; N=total patients in group; OR=odds ratio; RR=rate ratio; SQRQ-C= St. George's Respiratory Questionnaire COPD; UMEC=umeclidinium; VI=vilanterol; wk=week;

# Rate per patient year, calculated as the number of events divided by the total duration at risk

<sup>a</sup> Generalised linear model assuming a negative binomial distribution and covariates of treatment group, gender, exacerbation history ( $\leq 1$ ,  $\geq 2$  moderate/severe), smoking status (Screening), geographic region, post-bronchodilator percent predicted FEV1 (Screening).

<sup>b</sup> Cox proportional hazards model with covariates of treatment group, gender, exacerbation history ( $\leq 1$ ,  $\geq 2$  moderate/severe), smoking status (Screening), geographical region, and post-bronchodilator percent predicted FEV1 (Screening).

<sup>c</sup> Repeated measures model with covariates of treatment group, smoking status (Screening), geographical region, visit, baseline-by-visit, and treatment group-by-visit interactions.

<sup>d</sup> MCIDs used as the basis to define patients as responders or non-responders for various outcomes. Non-response included patients with a missing assessment with no subsequent non-missing on-treatment assessment for the outcome. Analysis excluded patients if baseline assessment of the outcome was missing or if the outcome value was missing but subsequent on-treatment outcome were present.

<sup>e</sup> Generalised linear mixed model with a logit link function and covariates of treatment group, smoking status (Screening), geographical region, visit, baseline, and baseline-by-visit and treatment-by-visit interactions.

Source: pp55-63 of the submission, Table 38, p150 and 39, p152 of IMPACT CSR.

6.10 For the comparison of ICS/LAMA/LABA versus LAMA/LABA, the PBAC noted that IMPACT demonstrated:

- The annual rates of moderate/severe exacerbation and severe exacerbation were significantly lower for FF/UMEC/VI compared to UMEC/VI, corresponding to a 25% (95%CI: 19%, 30%) and 34% (95%CI: 22%, 44%) reduction respectively, which are at the lower range of the nominated MCID (9% to 54%; for all grades of exacerbations). Relevant consideration of the baseline rate, exacerbation severity and study duration is required for interpretation of the MCID.
- There was a significantly larger improvement in trough FEV1, SCRQ-C score and CAT score at Week 52 compared to baseline for FF/UMEC/VI compared to UMEC/VI. Although the average effects were smaller than the nominated MCIDs, more patients were MCID “responders” with FF/UMEC/VI compared to UMEC/VI.
- There was significant reduction in the risk of all-cause mortality for FF/UMEC/VI compared to UMEC/VI. Despite the significant result, the trial was not powered to study survival and the trial design did not include mortality in its hierarchical testing procedure. The trial publication (Lipson et al 2018) interpreted the result as a signal toward lower mortality but emphasised that the finding may be “fragile”.

6.11 IMPACT also indicated that FF/VI was similar or slightly better on some outcomes (change from baseline in trough FEV1, St George's Respiratory Questionnaire COPD (SGRQ-C) total score and CAT score) compared to UMEC/VI. This evidence is

inconsistent with evidence considered in the Post-Market Review of COPD Medicines (2017) and previous PBAC decision-making, which suggested LAMA/LABAs are more efficacious than ICS/LABAs. These differences may be due to differences in trial design and selection criteria across trials directly comparing dual therapy.

- 6.12 The PBAC noted that the treatment effects in IMPACT were generally smaller than those estimated for FF/UMEC/VI versus any LAMA/LABA based on indirect comparisons considered by the PBAC in December 2017. For reduction in the annual rate of moderate/severe exacerbation: 25% (95%CI: 19%, 30%) in IMPACT versus 32% (95%CI: -3%, 66%) from indirect evidence. For difference in the mean change from baseline in trough FEV1 at Week 52: 54ml (95%CI: 39ml, 69ml) in IMPACT versus 117ml (67ml, 167ml) from indirect evidence.
- 6.13 A series of post-hoc subgroup analyses for key outcomes in IMPACT demonstrated the treatment effect was similar by baseline FEV1 % predicted plus exacerbation history, and prior treatment. The complementary subgroups by baseline FEV1 % predicted and exacerbation history were FEV1 <50% predicted and <2 moderate and no severe exacerbation in the prior year; FEV1 <50% predicted and  $\geq 2$  moderate or  $\geq 1$  severe exacerbation in the prior year; and FEV1  $\geq 50$ -<80% predicted and  $\geq 2$  moderate or  $\geq 1$  severe exacerbation in the prior year. This was based on the requested PBS population which includes currently eligible patients (FEV1 <50% predicted) as well as patients who will become eligible under the requested extension to the PBS listing (FEV1  $\geq 50$ % predicted). Subgroups analyses by prior COPD medication (at screening) included ICS/LABA/LAMA, LABA/LAMA and ICS/LABA.
- 6.14 The PBAC considered that, in the absence of formal testing, the results of the subgroup analysis supported the argument that FEV1 % predicted was not a good predictor of treatment benefit in terms of rate of moderate/severe exacerbation, change in trough FEV1 or SGRQ-C. The relative treatment effect was generally smaller for patients with “FEV1 <50% predicted, <2 moderate and no severe exacerbations” (i.e. fewer exacerbations at baseline). The treatment effect for patients on dual therapy at baseline was generally similar to the ITT population, but small patient numbers reduced statistical precision and confidence.
- 6.15 The ESC considered that the results of the IMPACT trial provided additional evidence for Trelegy versus dual therapy, reducing uncertainty around the claim of superior comparative effectiveness. However, the ESC noted that single therapy compared to triple therapy is not captured and, as already highlighted, there is a risk of Trelegy being used earlier than intended in the treatment pathway.

### **Comparative harms**

- 6.16 Table 5 summarises the main adverse events (AEs) reported in IMPACT. The incidence of on-treatment AEs, drug-related AEs and serious AEs were generally similar across

the groups. Overall, safety outcomes were consistent with known safety profiles for the use of an ICS, a LAMA, or a LABA in combination.

- 6.17 FF/UMEC/VI was associated with a higher incidence and exposure adjusted risk of pneumonia and oral candidiasis compared with UMEC/VI. In December 2017, the PBAC considered Trelegy was “likely to be associated with an increased risk of harms over dual therapy with LAMA/LABA, particularly in relation to pneumonia” (Paragraph 7.6, Trelegy PSD, December 2017). The PBAC noted that data from the subgroup analyses provided in Appendix 3 and 5 of the submission further indicated that patients with FEV1  $\geq 50$ - $<80\%$  and  $\geq 2$  moderate or  $\geq 1$  severe exacerbation in the prior year had [REDACTED] ([REDACTED], 95%CI: [REDACTED], [REDACTED]).

Table 5: Summary of key adverse events in the trials

Adverse event, n (%)	FF/UMEC/VI	UMEC/VI	FF/UMEC/VI vs UMEC/VI	
	N=4151	N=2070	RD (95%CI)	RR (95% CI)
Any AE	2897 (70)	1429 (69)	0.01 (-0.02, 0.03)	1.01 (0.98, 1.05)
Drug related <sup>#</sup>	478 (12)	214 (10)	0.01 (-0.00, 0.03)	1.11 (0.96, 1.30)
Non-fatal SAE	847 (20)	433 (21)	-0.01 (-0.03, 0.02)	0.98 (0.88, 1.08)
Frequently reported AEs ( $\geq 3\%$ in either treatment arms)				
Pneumonia	298 (7)	93 (4)	<b>0.03 (0.01, 0.04)</b>	<b>1.60 (1.27, 2.00)</b>
Oral candidiasis	161 (4)	41 (2)	<b>0.02 (0.01, 0.03)</b>	<b>1.96 (1.40, 2.75)</b>
Any MACE <sup>a</sup>	80 (2)	37 (2)	0.00 (-0.01, 0.01)	1.08 (0.73, 1.59)
n with $\geq 1$ bone fracture incident <sup>b</sup>	80 (2)	31 (1)	0.00 (-0.00, 0.01)	1.29 (0.85, 1.94)

Abbreviations: AE=adverse event; CI=confidence interval; FF=fluticasone fumarate; ITT=intention to treat; MACE=major adverse cardiac events; n=number of participants reporting data; N=total participants in group; RD=risk difference; RR= risk ratio; SAE=serious adverse event; UMEC=umeclidinium; VI=vilanterol;

<sup>#</sup> Investigator’s judgement of causality

<sup>a</sup> MACE narrow definition included only the PTs of non-fatal myocardial infarction and non-fatal acute myocardial in addition to central nervous system haemorrhages and cerebrovascular conditions SMQ excluding fatalities.

<sup>b</sup> If a subject suffered fractures in multiple locations with the same date of fracture, this was considered to be one fracture incident.

Source: Tables 29 to 33, pp63-70 of the submission.

- 6.18 The Pre-Sub-Committee Response (PSCR) reported that an additional adjudication process of all post-randomised serious AEs (fatal and non-fatal) did not indicate increased risk with Trelegy compared with UMEC/VI for pneumonia-related events. The ESC noted that the additional data on clinically adjudicated (hospitalised) pneumonia SAEs indicated similar pneumonia incidence across treatment groups (COPD exacerbation with evidence of pneumonia [REDACTED] (%) for Trelegy versus [REDACTED] (%) for UMEC/VI; Pneumonia without COPD exacerbation [REDACTED] (%) versus 21 ([REDACTED] %)). The ESC noted that the total number of pneumonia-related events had reduced from [REDACTED] to [REDACTED] during the adjudication process with a [REDACTED] % reduction in such events in the Trelegy arm and a [REDACTED] % reduction in the UMEC/VI arm. The ESC considered it was

unclear why there were such differential errors in reporting AEs in a double-blind, multi-centre study of about 10,000 participants. The pre-PBAC response argued that pneumonia AEs reported in Table 5 included broad definitions of pneumonia including non-hospitalised pneumonia while the adjudicated pneumonia definition focuses on the hospitalised and fatal pneumonia. The PBAC considered that inclusion of non-hospitalised pneumonia provides a more reliable assessment of the risks associated with the use of Trelegy and concluded that the claim of non-inferior safety could not be substantiated.

### ***Benefits/harms***

- 6.19 A summary of the comparative benefits and harms for FF/UMEC/VI versus UMEC/VI FDC is presented in Table 6 below.

**Table 6: Summary of comparative benefits and harms for FF/UMEC/VI and UMEC/VI**

IMPACT	FF/UMEC/VI	UMEC/VI	RR (95% CI)	Event rate/100 patients		RD (95% CI)
				FF/UMEC/VI	UMEC/VI	
<b>Benefits</b>						
Annual rate of on-treatment exacerbation						
Moderate/severe	0.91 (0.87, 0.95)	1.21 (1.14, 1.29)	<b>0.75 (0.70, 0.81)</b>	91	121	<b>-0.30 (NR)</b>
Severe	0.13 (0.12, 0.14)	0.19 (0.17, 0.22)	<b>0.66 (0.56, 0.78)</b>	13	19	<b>-0.06 (NR)</b>
Patients with on-treatment exacerbations						
Moderate	1719/4151	887/2070	0.97 (0.91, 1.03)	41	43	-0.01 (-0.04, 0.01)
Severe	447/4151	272/2070	<b>0.82 (0.71, 0.94)</b>	11	13	<b>-0.02 (-0.04, -0.01)</b>
Moderate/severe	1959/4151	1036/2070	<b>0.94 (0.89, 1.00)</b>	47	50	<b>-0.03 (-0.05, -0.00)</b>
Trough FEV1 responders at Week 52 (with ≥100mL increase from baseline)						
Responders	1561/4138	561/2068	<b>1.39 (1.28, 1.51)</b>	38	27	<b>0.11 (0.08, 0.13)</b>
SGRQ-C responders at Week 52 (total score ≤4 units below baseline)						
Responders	1723/4108	696/2050	<b>1.24 (1.15, 1.33)</b>	42	34	<b>0.08 (0.05, 0.11)</b>
CAT responders at Week 52 (CAT score ≤2 units below baseline)						
Responders	1698/4076	730/2034	<b>1.16 (1.08, 1.24)</b>	42	36	<b>0.06 (0.03, 0.08)</b>
<b>Harms</b>						
Any AE	2897/4151	1429/2070	1.01 (0.98, 1.05)	70	69	0.01 (-0.02, 0.03)
Drug related	478/4151	214/2070	1.11 (0.96, 1.30)	12	10	0.01 (-0.00, 0.03)
Non-fatal SAE	847/4151	801/2070	0.98 (0.88, 1.08)	20	19	-0.01 (-0.03, 0.02)
Pneumonia	298/4151	93/2070	<b>1.60 (1.27, 2.00)</b>	7	4	<b>0.03 (0.01, 0.04)</b>
Oral candidiasis	161/4151	41/2070	<b>1.96 (1.40, 2.75)</b>	4	2	<b>0.02 (0.01, 0.03)</b>

Abbreviations: CAT=COPD Assessment Test; CI=confidence interval; FEV1=forced expiratory volume in one second; FF=fluticasone fumarate; HR = hazard ratio; ITT=intention to treat; n=number of participants reporting data; N=total participants in group; RD=risk difference; RR= risk ratio; SAE=serious adverse event; SGRQ-C= St. George's Respiratory Questionnaire COPD; UMEC=umeclidinium; VI=vilanterol; Source: Section 2.5.1, pp55-72 and Tables 29 to 33, pp63-70 of the submission and Table 38, p150 and 39, p152 of IMPACT CSR

6.20 On the basis of direct evidence presented by the submission, for every 100 patients treated with FF/UMEC/VI versus UMEC/VI over 52 weeks:

- Approximately 30 fewer moderate or severe exacerbations per year on treatment (25% reduction in the number of moderate or severe exacerbations)
- Approximately 6 fewer severe exacerbations per year on treatment (34% reduction in the number of severe exacerbations)
- Approximately 3 fewer patients would have moderate or severe exacerbation;

- Approximately 2 fewer patients would have severe exacerbation;
- Approximately 11 more patients would have improved lung function measured by trough FEV1 ( $\geq 100$  mL increase from baseline);
- Approximately 8 more patients would have improved in their COPD health status on the SGRQ-C score ( $\leq 4$  units below baseline);
- Approximately 6 more patients would have improved in their COPD health status impairment measured on the CAT score ( $\leq 2$  units below baseline);
- Approximately 3 more patients would experience pneumonia;
- Approximately 2 more patients would experience oral candidiasis.

### ***Clinical claim***

- 6.21 The submission described Trelegy as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety compared with dual therapy LAMA/LABA, informed by UMEC/VI. Data from IMPACT supports the claim of superior efficacy but not the claim of non-inferior safety. FF/UMEC/VI was associated with higher incidence of pneumonia and oral candidiasis compared to UMEC/VI, in-line with the known safety profile of FF and other ICS drugs. The ESC considered the results of IMPACT supported the claim of superior efficacy but noted that the statistically significant increase in the investigator-reported incidence of pneumonia and oral candidiasis did not substantiate the claim of non-inferior safety. The ESC noted the differential errors in reporting pneumonia-related AEs highlighted by the data presented in the PSCR and considered that the additional data provided did not alleviate the uncertainty around the claim of non-inferior safety.
- 6.22 The PBAC considered that the claim of superior comparative effectiveness over LAMA/LABA dual therapy was reasonable.
- 6.23 The PBAC considered that the claim of non-inferior comparative safety compared to LAMA/LABA dual therapy was not adequately supported by the data, and that triple therapy had inferior safety to LAMA/LABA dual therapy.

### ***Economic analysis***

- 6.24 The resubmission presented a cost utility analysis based on results from IMPACT (ITT) to justify the inclusion of moderate COPD patients in the proposed PBS population, as summarised in Table 7. The ITT population included patients currently eligible (i.e. FEV1  $< 50\%$  predicted) and ineligible (i.e. FEV1  $\geq 50\%$ – $< 80\%$  predicted) for Trelegy.

**Table 7: Key components of the economic evaluation**

Component	Description
Type of analysis	Cost-utility analysis
Outcomes	Life years gained, quality-adjusted life years
Time horizon	10 years in the model base case vs. 1 year in the key trial
Methods used to generate results	Trial-based decision tree (1 year) then Markov model (9 years)
Health states	Model includes 7 health states based on FEV1% predicted category and history of recent exacerbations within the past year, as well as dead. <ul style="list-style-type: none"> <li>- FEV1% 50&lt;80 ('moderate' COPD), no recent history of exacerbations (&lt;12m)</li> <li>- FEV1% 50&lt;80 ('moderate' COPD), recent history of exacerbations (&lt;12m)</li> <li>- FEV1% 30&lt;50 ('severe' COPD), no recent history of exacerbations (&lt;12m)</li> <li>- FEV1% 30&lt;50 ('severe' COPD), recent history of exacerbations (&lt;12m)</li> <li>- FEV1% &lt;30 ('very severe' COPD), no recent history of exacerbations (&lt;12m)</li> <li>- FEV1% &lt;30 ('very severe' COPD), recent history of exacerbations (&lt;12m)</li> <li>- Dead</li> </ul>
Cycle length	1 year (half-cycle corrected)
Transition probabilities	A post-hoc analysis of the IMPACT trial informs the distribution across the health states at 1 year. Two regressions estimated from TORCH (a 3 year RCT) and mortality estimates from Afonso et al 2011 inform the transition across the health states thereafter in the Markov model. The first regression of TORCH data estimates the decline in FEV1 over time as a function of recent exacerbations. The second regression of TORCH data estimates the rate of exacerbations as a function of FEV1% predicted and recent exacerbations.
Utilities	Trial-based utility by treatment arm; utilities for FEV1% predicted health states informed by Rutten-van Molken et al 2006; disutility for clinical events informed by NICE COPD guidelines 2012.
Costs	Included costs associated with treatment, replacement therapy (discontinuation), maintenance, exacerbation and pneumonia.
Software package	Microsoft Excel.

Abbreviations: COPD=chronic obstructive pulmonary disease; FEV1=forced expiratory volume in one second; FF=fluticasone fumarate; RCT=randomised controlled trial; UMEC=umeclidinium; VI=vilanterol.

Source: Table 52, p108 of the submission

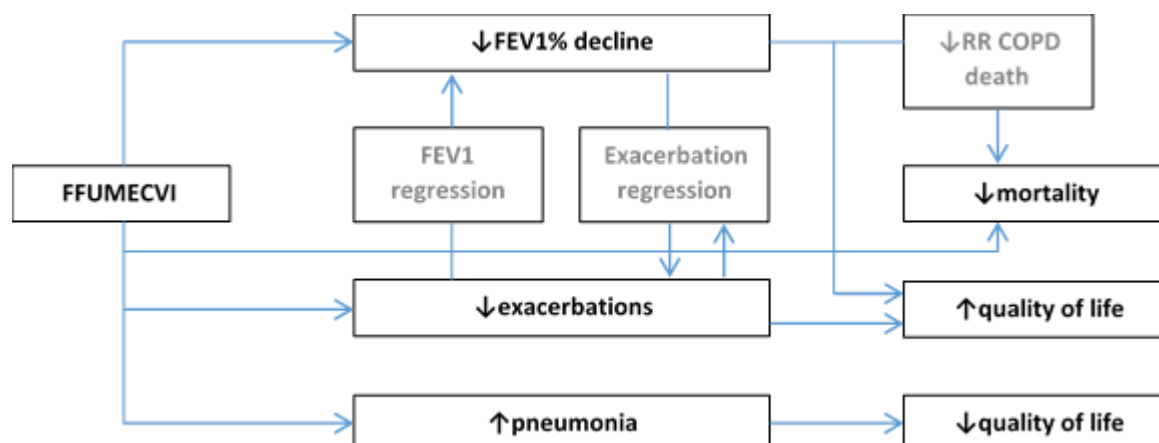
6.25 The modelled analysis consisted of a short-term trial-based model based on costs and outcomes measured in IMPACT (1 year) and a long-term Markov model to extrapolate costs and outcomes into the future (to 10 years).

6.26 Short-term trial-based model: Post-hoc analysis of IMPACT trial data informed the proportion of patients starting in each of the three FEV1 % predicted health states at Week 0 and the proportion of patients in each of the FEV1 % predicted health states with and without recent exacerbation at Week 52. Within trial mortality was used to adjust the distribution across the health states at Week 52. The post-hoc analysis also informed the proportion of patients who discontinued treatment by Week 52, and the

number of moderate exacerbations, severe exacerbations and episodes of pneumonia. Patients could discontinue treatment and commence replacement therapy (any COPD medication) based on IMPACT. The ESC noted that the majority of the treatment effect occurred within the first twelve months of the model.

- 6.27 Long-term Markov model: Patients commenced in the Markov model in the corresponding health state at the end of the trial-based model. In each model cycle, patients either remained in the same FEV1 % predicted health state, transitioned to the subsequent and more severe FEV1 % predicted health state, or died. The proportion of patients with acute exacerbation in the previous cycle determined the distribution across the FEV1 % predicted health states with or without recent history of exacerbation. Patients could also experience an acute episode of pneumonia in each cycle that did not impact on mortality or other transitions. There was no further treatment discontinuation in the Markov model.
- 6.28 The treatment effect in the trial-based model were the direct effects reported in IMPACT, including fewer exacerbations, improved mortality and better lung function causing a one-time shift in the distribution of the population across health states. The model calculated trial-based quality adjusted life years (QALYs) directly from IMPACT EQ-5D data by estimating the area under the curve at Week 26 and Week 52, adjusted for disutility associated with exacerbation and pneumonia. The submission did not present the full methodology or the adjustment for disutility, and so there may be some potential for double counting given the EQ-5D likely incorporated some disutility associated with clinical events. The methodology also likely incorporated the small survival benefit for triple therapy reported in IMPACT, which was considered “fragile”. However, the ESC agreed that the incremental QALY gain of █████ in the trial period appeared reasonable. The PSCR stated that the trial-based and Markov models applied disutility due to exacerbation and pneumonia in the same way. The PSCR also stated that with EQ-5D data collected at only two-time points, the potential for double counting is minimal. The ESC agreed the impact of double counting appeared to be minimal.
- 6.29 In the Markov component, the submission assumed no direct effects on exacerbations, mortality or lung function. However, the shift in the health state distributions after the trial could have indirect effects on exacerbation, mortality and lung function over time. For example, fewer exacerbations resulted in slower FEV1 % predicted decline and fewer future exacerbations; slower FEV1 % predicted decline resulted in fewer exacerbations and mortality, summarised in Figure 1. The Markov model calculated QALYs based on utility weights in the literature.

Figure 1: Treatment effects in the modelled evaluation



Source: Constructed during the evaluation

6.30 Table 8 provides a summary of the key drivers in the modelled economic evaluation.

Table 8: Key drivers of the model

Description	Method/Value	Impact
Health state distribution at Week 52	The model uses IPD from IMPACT to estimate the change in the six FEV1 % predicted-exacerbation health states at Week 52, which are extrapolated over the time horizon. Trial-based QALYs calculated from area under the curve in IMPACT, including mortality differences and adjustments for exacerbations and pneumonia.	Uncertainty in trial outcomes was not tested <sup>a</sup>
Pneumonia disutility	Model assumed disutility for pneumonia was -0.01 (NICE 2012). Updated estimate was much larger at -0.13 (NICE 2018).	Moderate, favours Trelegy
Replacement therapy costs	Model inappropriately assumed majority of patients who discontinued dual therapy in the model commenced the more costly triple therapy, based on replacement therapy in IMPACT.	Moderate, favours Trelegy
Cost of treating pneumonia	The model inappropriately underestimated hospital costs associated with treating pneumonia by dividing total costs by average length of stay. Correcting this error increases the cost of treating pneumonia in hospital by a factor of [redacted].	Moderate, favours Trelegy

<sup>a</sup> Uncertainty in trial outcomes was not tested because the submission did not provide the IPD.

IPD = Individual patient data

Source: compiled during the evaluation

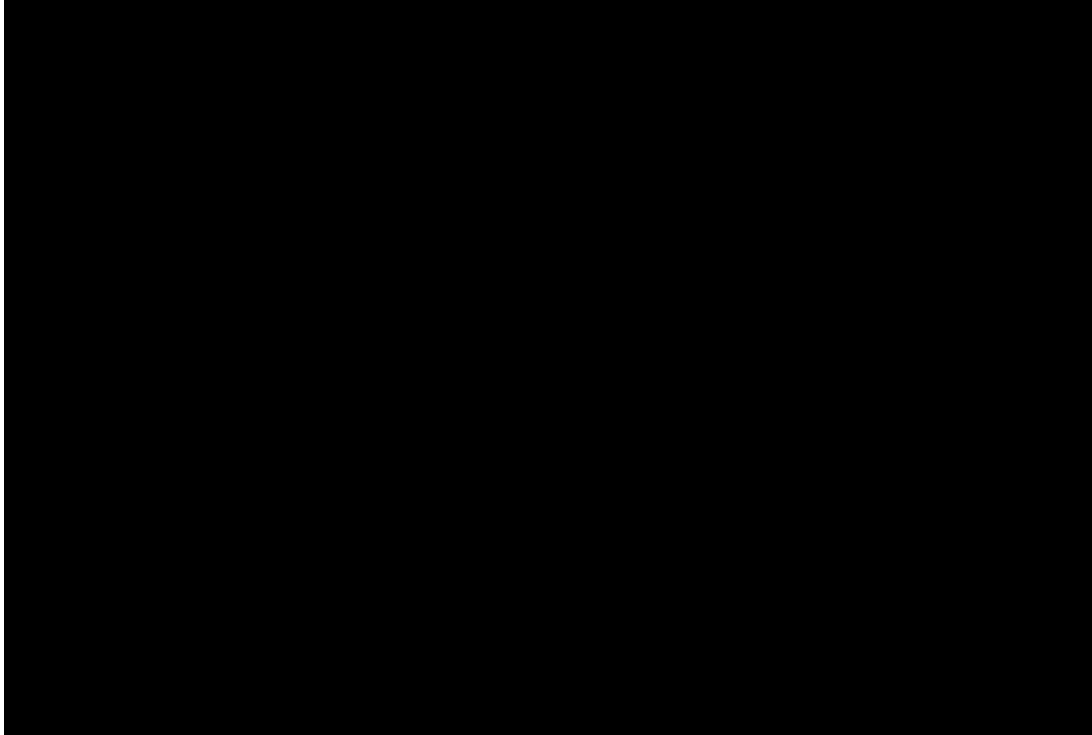
6.31 Overall, the main driver of benefits in the model was the shift in the FEV1 % predicted health states in favour of Trelegy (ICS/LAMA/LABA) at Week 52, as well as the reduction in the number of exacerbations (moderate and severe) during the trial period. However, uncertainty around these parameters was not testable given the structure of the modelled evaluation. The PSCR stated that the distribution of health states at the beginning of the Markov model was user adjustable for sensitivity testing such that uncertainty around these parameters could be tested. The ESC noted that the uncertainty in trial outcomes was not tested as the submission did not provide the individual patient data required. For example, the ESC noted that re-sampling the health state distributions requires information about the joint distributions of change in FEV1% predicted and exacerbations.

- 6.32 The size of any indirect effects in the Markov model were negligible given there was no difference in the proportion of patients with any exacerbation at Week 52 in the post-hoc IMPACT analysis (in contrast to the ITT results). The increase in the risk of pneumonia resulted in a small disutility over the time horizon.
- 6.33 The ESC considered that, in addition to underestimating disutility for pneumonia, another key driver of the model was underestimation of pneumonia hospitalisation costs. The ESC noted that for the treatment of pneumonia, the submission assumed treatment required hospitalisation (■%) or an emergency department visit (■%) based on data in IMPACT, costed using AR-DRGs. In contrast to the estimation of treatment costs for an exacerbation, the submission divided the inpatient DRG for pneumonia by the average length of stay. The ESC noted that the submission did not justify this assumption, which likely underestimated the cost of pneumonia treatment in hospital by a factor of 4.24 (average length of stay for E62A and E62B, 5.94 and 2.54 days respectively). The PSCR acknowledged the error in the calculation of the cost of hospitalised pneumonia and confirmed that correcting this error increased the ICER to \$15,000/QALY to \$45,000/QALY over the 10 year time horizon.
- 6.34 The main cost offsets in trial-based analysis were due to exacerbation (-\$■) and replacement therapy (-\$■), whereas the main cost offsets in the Markov model extrapolation were due to replacement therapy (-\$■) and maintenance costs (-\$■). Difference between the trial based and modelled economic evaluation estimates on cost offsets were due to time horizon and the inappropriate assumption in the Markov model that the majority of patients who discontinue dual therapy would commence the more costly triple therapy, based on replacement therapy in IMPACT. This assumption was not reasonable given the model intended to estimate cost-effectiveness of triple therapy ICS/LAMA/LABA compared to no triple therapy (i.e. dual therapy LAMA/LABA only), and model inputs from IMPACT were by definition “on-treatment”. The PSCR provided data on the efficacy of FF/UMEC/VI compared to ICS/LABA (from IMPACT and FULFIL trials) and UMEC/VI (from IMPACT) to justify the assumption that patients who discontinued LAMA/LABA would commence treatment on multiple-inhaler triple therapy (MITT) rather than switch to ICS/LABA. Given the model intended to estimate the cost-effectiveness of triple therapy ICS/LAMA/LABA (FDC or MITT) versus a world without triple therapy (i.e. dual therapy LAMA/LABA only), the ESC considered it was not reasonable to include cost-offsets in the model associated with patients who discontinued dual therapy and step up to triple therapy. The ESC noted that the treatment effect in the model was the “on-treatment” treatment effect, and hence the model should not include benefits for patients who stepped up from dual to triple therapy in the LAMA/LABA arm. The ESC noted this issue to be the key concern associated with the model structure. The ESC noted that when replacement therapy costs were removed from the Markov model and it was assumed patients would instead switch from LAMA/LABA to ICS/LABA the ICER increased to less than \$15,000/QALY from a base case of less than \$15,000/QALY. The

pre-PBAC response disagreed with the ESC and argued that the intent of the model is to estimate cost-effectiveness of triple therapy when used earlier in the treatment algorithm since triple therapy is currently Guideline supported and PBS approved for use later in the treatment algorithm. The pre-PBAC response also argued that the model was conservative as treatment switches only occur in year 1, whereas in practice there would be more switch to triple therapy with COPD progression over the 10-year duration of the model. The PBAC noted that, as the model aimed to compare treatment with dual therapy compared to treatment with triple therapy, the benefits for patients stepped up from dual to triple therapy in the LAMA/LABA arm were appropriately not included in the model and hence agreed with the ESC that the cost-offsets associated with such a treatment switch should also not be included in the model.

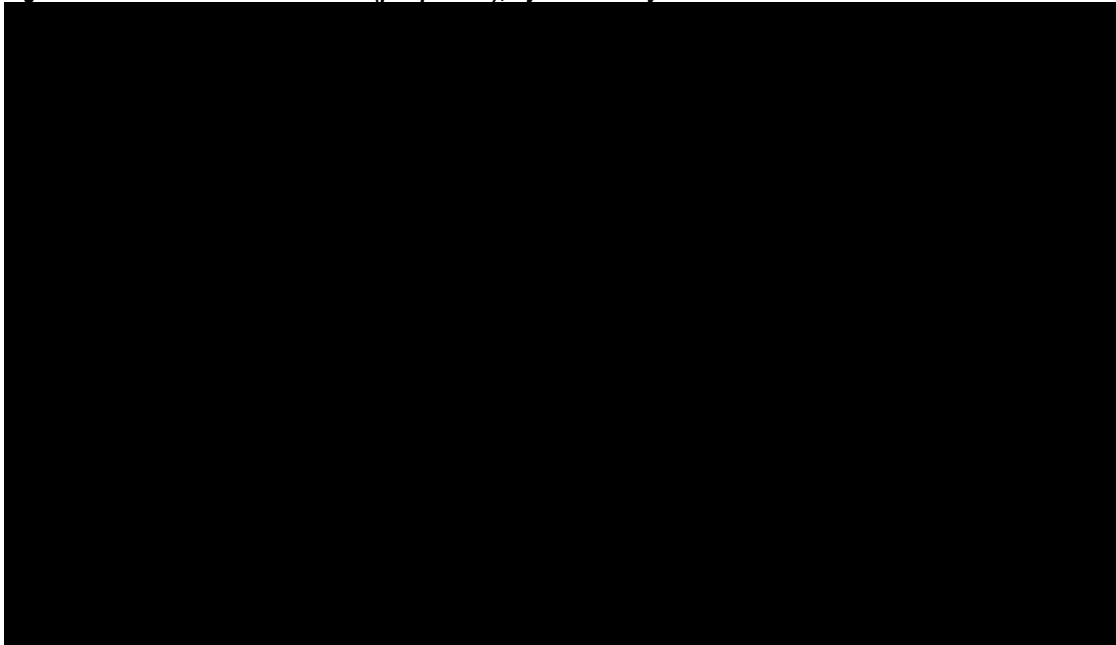
- 6.35 Although there were a number of small additional discrepancies and errors identified during the evaluation, ultimately the model was not particularly sensitive to them. These included model parameters derived from the post-hoc analysis of IMPACT that did not match the ITT results (proportion of deaths, proportion of discontinuations, and proportion with any moderate/severe exacerbation). The submission also incorrectly interpreted a regression coefficient for “recent exacerbation history” as a slope coefficient, overestimating the rate of FEV1 decline associated with recent exacerbation.
- 6.36 Figures 2 and 3 present traces of the FEV1 % predicted health states and number of clinical events in the model. The figures illustrate the shift in FEV1 % predicted health states in favour of Trelegy (ICS/LAMA/LABA) in the trial-based period, as well as the reduction in the number of exacerbations (moderate and severe) and increase in cases of pneumonia.

**Figure 2: Markov trace of FEV1 % predicted health states and proportion with any exacerbation, by arm and cycle**



Abbreviations: COPD=chronic obstructive pulmonary disease; FEV1=forced expiratory volume in one second; FF=fluticasone fumarate; mod=moderate COPD; sev=severe COPD; v.sev=very severe COPD; UMEC=umeclidinium; VI=vilanterol.  
Source: constructed during the evaluation using Attachment 3 Cost effectiveness model\_Sect 3.xlsm.

**Figure 3: Number of clinical events (per person), by arm and cycle**



Abbreviations: FEV1=forced expiratory volume in one second; FF=fluticasone fumarate; UMEC=umeclidinium; VI=vilanterol;  
Source: constructed during the evaluation using Attachment 3 Cost effectiveness model\_Sect 3.xlsm.

6.37 Table 9 provides the results of the stepped economic evaluation as presented in the submission. The results indicated Trelegy (FF/UMEC/VI) was dominant compared to UMEC/VI over the trial-based period, and had an ICER less than \$15,000/QALY over 10 years. The ESC considered a more reliable base case should include revised pneumonia hospitalisation costs and discontinuation from LAMA/LABA to ICS/LABA instead of triple therapy. This increased the ICER to \$15,000/QALY to \$25,000/QALY over the 10 year modelled time horizon. The PBAC agreed that the revised base case proposed by the ESC was appropriate.

**Table 9: Results of the stepped economic evaluation (ITT population)**

Step and component	Proposed medicine	Comparator	Increment
<b>Step 1: Trial-based costs and outcomes (Year 1)</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	-\$ [REDACTED]
LYG	[REDACTED]	[REDACTED]	[REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra LYG gained			[REDACTED]
Incremental cost/extra QALY gained			-\$ [REDACTED]
<b>Step 2: Markov model costs and outcomes (Years 2 to 10)</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYG	[REDACTED]	[REDACTED]	[REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra LYG gained			\$ [REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
<b>Step 3: Combined model costs and outcomes (Years 1 to 10)</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYG	[REDACTED]	[REDACTED]	[REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra LYG gained			\$ [REDACTED]
<b>Incremental cost/extra QALY gained (base case)</b>			\$ [REDACTED]
<b>Incremental cost/extra QALY gained (ESC revised base case)</b>			\$ [REDACTED]

Source: Tables 70 to 73, pp136-137 of the submission.

6.38 The submission did not present any external validation of model outputs. However, a structurally different modelled analysis of IMPACT data considered by CADTH (2018) estimated similar incremental QALYs. In that model, triple therapy FF/UMEC/VI resulted in an additional [REDACTED] QALYs versus UMEC/VI over a lifetime model horizon. In the modelled analysis presented in the submission, triple therapy resulted in an additional [REDACTED] QALYs gained over the same time horizon. Limited reporting

precluded any comparison of incremental costs between the two models; higher incremental cost in the CADTH model (CAN\$ [REDACTED]<sup>1</sup> versus AU\$ [REDACTED] over a lifetime) may have been driven partly by a higher requested price for FF/UMEC/VI in Canada (annual drug cost of CAN\$1,608<sup>2</sup> vs AU\$ [REDACTED]).

6.39 Table 10 presents the results of the sensitivity analyses. The results indicated that the model was most sensitive to the cost offsets for replacement therapy and the cost of treating cases of pneumonia. The ESC noted that the sensitivity analyses presented in Table 10 was based on a base case of less than \$15,000/QALY not the ESC revised base case of \$15,000/QALY to \$45,000/QALY.

**Table 10: Results of other sensitivity analyses coded into the model and conducted during the evaluation**

Analyses	Incremental cost	Incremental QALY	ICER
<b>Base case (ITT)</b>	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Post-trial treatment effect for 5 years without waning	-\$ [REDACTED]	[REDACTED]	[REDACTED]
Post-trial treatment effect for 5 years with waning	-\$ [REDACTED]	[REDACTED]	[REDACTED]
Time horizon – lifetime	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
No within trial mortality (within trial utility on)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
No within trial mortality (within trial utility off)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
<i>No increased rate of FEV1 % predicted decline for recent exacerbation</i>	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
<i>NICE 2018 disutility estimates for clinical events</i>	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
<i>Discontinuation from LAMA/LABA to ICS/LAMA, not triple therapy</i>	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
<i>No cost associated with discontinuation</i>	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
<i>No length of stay adjustment to DRG for pneumonia</i>	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
<b>Current PBS subgroup (FEV1&lt;50% predicted &amp; ≥2 exacerbations)</b>	\$ [REDACTED]	[REDACTED]	[REDACTED]

Abbreviations: FEV1=forced expiratory volume in one second; ICER=incremental cost effectiveness ratio; ICS=inhaled corticosteroid; ITT=intention to treat; LABA=long-acting beta-2 agonist; LAMA=long-acting muscarinic antagonist; QALY=quality adjusted life year; Source: Constructed during the evaluation; Attachment 3 Cost effectiveness model\_Sect 3.xlsm

6.40 Results for the subgroup in IMPACT defined by current PBS criteria (defined as FEV1<50% predicted and ≥2 exacerbations in past 12 months) indicated that triple therapy was dominant compared to dual therapy with a greater improvement in QALYs. Although the submission did not present results for the complement, that is patients currently ineligible for PBS treatment (FEV1 ≥50% predicted), the results imply that treatment would not be as effective or cost-effective in those patients.

<sup>1</sup> AU\$ [REDACTED] based on the exchange rate of 1 CAD = 1.0494 AUD at 7 January 2019.

<sup>2</sup> AU\$ [REDACTED] based on the exchange rate of 1 CAD = 1.0494 AUD at 7 January 2019.

- 6.41 The ESC noted that the potential for Trelegy use earlier in the treatment pathway was not captured in the model. The ESC considered that a more informative model would take this into account to determine if triple therapy is cost effective not only to dual therapy, but also to single therapy and to no therapy.

**Drug cost/patient/year: \$" (Trelegy)**

- 6.42 The model estimated the cost of Trelegy (FF/UMEC/VI) per patient per year on treatment was \$ (364 days). The incremental cost of FF/UMEC/VI versus UMEC/VI per patient per year on treatment was \$ (364 days).

**Estimated PBS usage & financial implications**

- 6.43 This submission was not considered by DUSC.
- 6.44 The submission applied both an epidemiological and market share approach to generate utilisation and financial estimates for the proposed change to Trelegy's PBS listing.
- 6.45 The financial estimates presented in the submission assumed Trelegy will only substitute for LAMA/LABA FDC products in a proportion of patients still experiencing repeated exacerbation. This is reasonable based on the rationale that patients on ICS/LABA combination can already access Trelegy on the PBS given they would have already satisfied the clinical criteria (i.e., FEV1 <50% predicted).

Public Summary Document – March 2019 PBAC Meeting

**Table 11: Estimated use and financial impact of the proposed change to Trelegy PBS listing**

Description	Year 1 2019	Year 2 2020	Year 3 2021	Year 4 2022	Year 5 2023	Year 6 2024
<b>Number of PBS/RPBS scripts for Trelegy</b>						
PBS	█	█	█	█	█	█
RPBS	█	█	█	█	█	█
Total PBS/RPBS	█	█	█	█	█	█
<b>Total cost of Trelegy at DPMQ</b>						
PBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Total PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
<b>Patient copayments for Trelegy</b>						
PBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Total PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
<b>Total additional cost to PBS/RPBS for Trelegy at DPMQ (net of patient copayments)</b>						
PBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Total PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
<b>PBS cost offset from reduced use of LAMA/LABA (net of patient copayments)</b>						
PBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Total PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
<b>Net cost due to listing of additional population for Trelegy</b>						
PBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Total PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Cost offsets for avoiding moderate exacerbations (antibiotics, systemic steroids, oxygen)	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)
MBS savings for reduced visits for exacerbations	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)
<b>Net impact to Government Budget</b>	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █

Abbreviations: DPMQ=dispensed price maximum quantity; FF=fluticasone furoate; PBS=pharmaceutical benefits scheme; RPBS=repatriation pharmaceutical benefits scheme; UMEC=umeclidinium; VI=vilanterol;

Source: Trelegy Ellipta Utilisation and Cost Model Workbook, Table 86-88, pp156-160 of the submission.

6.46 The ESC noted that the financial estimates were most sensitive to assumptions around Trelegy uptake and LAMA/LABA proportional market share of the overall COPD

maintenance therapies on PBS. These inputs feed into the calculation of eligible and treated patients on Trelegy. The submission's estimates do not account for cost offsets associated with reduction of severe exacerbations, which is conservative.

- 6.47 The PBAC noted the submission's estimated budget impact is in addition to the net expenditure in the population approved in the December 2017 submission, in which the estimated net total cost just less than \$10 million over six years of listing. The PBAC noted the amendments to the proposed restriction outlined in paragraph 2.4 and considered that it was reasonable to accept the financial estimates as the basis for an increase in the financial cap of the existing Risk Sharing Arrangement.
- 6.48 The submission also suggested the removal of the spirometric requirement would be applicable to PBS listed ICS/LABA FDCs. Although no consideration was given in the financial estimates on the implication of this suggested change, it is expected that more patients would be able to access these treatments since a barrier to the next lines of therapies is removed and this could have utilisation implications for all COPD maintenance therapies on PBS. The submission's approach (focusing only on substitution of LAMA/LABA FDCs) does not allow these dynamics to be considered. The PBAC noted that the proposed removal of the FEV1 criteria of the COPD indication for all ICS/LABA FDC products would be accompanied by changes to the clinical criteria as outlined in paragraph 2.5. As such, the PBAC considered it less likely that removal of the FEV1 criteria for ICS/LABA FDC products would have a significant impact on utilisation of COPD maintenance therapies.

### ***Quality Use of Medicines***

- 6.49 The submission presented a number of quality of use of medicine activities engaged by the sponsor (completed and ongoing) with clinicians to provide clarity on medicine choices in COPD as well as data on classification of medication errors reported for Trelegy (as per TGA documents and the Periodic Benefit Risk Evaluation Report (PBRER) for 18 September 2017 to March 2018). From limited data received so far, no significant safety information on patterns of medication error have been identified.
- 6.50 The ESC highlighted concerns regarding use of Trelegy earlier in the treatment pathway than intended along with risks associated with concomitant use of both Trelegy and other mono or dual therapy inhalers as potential quality use of medicines issues. Conversely, the ESC noted that there may be potential safety benefits of being on one inhaler compared with being on multiple inhalers, which may be of benefit for many patients with COPD. The PBAC noted that in its December 2017 consideration of Trelegy it had recommended a DUSC review of Trelegy be conducted two years after listing to explore whether triple therapy market growth had been appropriate.
- 6.51 The PBAC noted that removal of the clinical criteria restricting access to patients with a FEV1 of < 50% predicted would be consistent with GOLD recommendations but not current COPD-X guidelines. The PBAC noted that such inconsistency may lead to

potential prescriber confusion. The PBAC was also concerned that removal of the FEV1 criteria could be seen to undermine the importance of spirometry in the diagnosis and monitoring of COPD.

- 6.52 While there are currently no imposed post-marketing efficacy studies planned for Trelegy, the submission stated that a number of pharmacovigilance studies are either completed, currently ongoing or were planned for FF/VI and UMEC/VI. These range from studies considering cardiovascular and cerebrovascular side effects of UMEC/VI compared to tiotropium, bone mineral density effects of ICS in FF/VI versus VI alone to a study considering “real world” experience with UMEC/VI and UMEC post market.

### **Financial Management – Risk Sharing Arrangements**

- 6.53 In the December 2017 consideration of Trelegy, the PBAC recommended a Risk Sharing Arrangement for Trelegy to address uncertainties associated with cost effectiveness, 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. The resubmission [REDACTED]

[REDACTED]. The ESC noted that the PSCR modified the request stating that the evidence provided in the submission ‘supports an expansion of the use of Trelegy to patients with FEV1>50% currently not incorporated in the existing risk share arrangement. Consequently, the risk share arrangement, if not removed, should at least be adjusted to include the expanded cost-effective population that would derive clinical benefit.’ The ESC considered that it may be reasonable to slightly increase the existing caps, pending review of stable utilisation data for Trelegy once available.

- 6.54 Despite presentation of cost effectiveness data for triple versus dual maintenance therapy (LAMA/LABA) in COPD, uncertainties associated with 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 remain.
- 6.55 The ESC noted that the submission did not present any cost effectiveness data for triple therapy versus LAMA monotherapy or examine potential utilisation changes across the whole COPD market. Furthermore, the ESC considered that given the usage for Trelegy on PBS is not yet stable, it would be difficult to determine whether the existing caps will be breached in the first or subsequent years. The pre-PBAC response argued that whether the existing caps will be breached or Trelegy use is stable are not relevant to the requested change to the risk share as the current Risk Sharing Arrangement does not incorporate use in the expanded population.

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

## 7 PBAC Outcome

- 7.1 The PBAC recommended an extension to the existing Authority Required (STREAMLINED) listing of fluticasone furoate with umeclidinium and vilanterol (Trelegy) for COPD, specifically the removal of the FEV1 threshold from the clinical criteria in the restriction.
- 7.2 The PBAC was satisfied that Trelegy provides, for some patients, a significant improvement in efficacy over dual therapy (LAMA/LABA).
- 7.3 The PBAC recommended the removal of the FEV1 threshold from the Trelegy clinical criteria noting the change to be consistent with recent amendments to the GOLD guidelines (2018). The PBAC considered that the GOLD guidelines reflect current evidence indicating that FEV1 lacks precision to be used clinically as a predictor of exacerbations or mortality in patients with COPD and noted that history of previous exacerbations is regarded as the best predictor of future COPD episodes. As such, the PBAC considered that the removal of the FEV1 threshold should be accompanied by a strengthening of the clinical criteria to include specification of exacerbation severity and a 12 month time period for the exacerbation history. In addition, the PBAC recommended the restriction retain reference to the requirement for a patient to be experiencing significant symptoms despite LAMA/LABA therapy. The PBAC also considered that the restriction should include reference to the importance of spirometry in the diagnosis of COPD.
- 7.4 The PBAC noted that the Australian COPD-X Guidelines (December, 2018) use FEV1 to classify COPD severity. The PBAC was concerned that the inconsistency between the GOLD and COPD-X guidelines may cause prescriber confusion. The PBAC considered that the current recommendations of the COPD-X guidelines were likely influenced by the PBS criteria for subsidy. The PBAC recommended that the PBAC Secretariat write to the organisations responsible for updating the COPD-X guidelines (Lung Foundation Australia and the Thoracic Society of Australia and New Zealand) advising them of the PBAC's recommendations in relation to the Trelegy restriction and of the PBAC concerns about maintaining consistency between the COPD-X Guidelines and the PBS prescribing criteria.
- 7.5 The PBAC considered that LAMA/LABA dual therapy was an appropriate comparator.
- 7.6 The PBAC noted that the submission primarily used evidence from the IMPACT trial to establish the effectiveness of the Trelegy in the broader population (i.e. currently eligible patients (FEV1 < 50% predicted) as well as patients who will become eligible under the requested extension to the PBS listing (i.e. FEV1 ≥ 50% predicted)). The PBAC considered that the IMPACT trial results indicate that Trelegy is associated with improved efficacy in terms of lung function and exacerbations over dual therapy with LAMA/LABA. However, the PBAC noted that the treatment effects in IMPACT were generally smaller than those estimated for FF/UMEC/VI versus any LAMA/LABA based on the indirect comparisons considered by the PBAC in December 2017.

- 7.7 The PBAC, whilst noting the smaller treatment effect in the IMPACT trial, advised that the results of the subgroup analysis supported the argument that FEV1 % predicted is not a good predictor of treatment benefit in terms of rate of moderate/severe exacerbation, change in trough FEV1 or SGRQ-C.
- 7.8 The PBAC noted the increased incidence of pneumonia and oral candidiasis associated with Trelegy versus UMEC/VI reported in the IMPACT trial. The PBAC reaffirmed its December 2017 advice that triple therapy with Trelegy was 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 reaffirmed that the appropriate place in therapy for Trelegy should be following inadequate control with dual therapy.
- 7.9 In considering the cost-effectiveness of Trelegy the PBAC noted that a correction for pneumonia costs was acknowledged and accepted by the sponsor increasing the base case ICER to \$15,000/QALY to \$45,000/QALY over the 10 year time horizon. However, the PBAC agreed with the ESC that a more reliable base case should include both revised pneumonia hospitalisation costs and discontinuation from LAMA/LABA to ICS/LABA instead of triple therapy. The PBAC considered the resulting ICER of \$15,000/QALY to \$45,000/QALY over the 10 year modelled time horizon to be acceptable and concluded it was reasonable to accept the cost-effectiveness of Trelegy in the requested PBS population.
- 7.10 The PBAC noted the financial estimates proposed for Trelegy in this submission are in addition to the net expenditure approved in the December 2017 submission. The PBAC considered that the overall estimated budget impact was relatively low.
- 7.11 The PBAC recalled that in December 2017 it had recommended a Risk Sharing Arrangement for Trelegy to address uncertainties associated with 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. The PBAC considered that a Risk Sharing Arrangement remained appropriate to mitigate any residual uncertainties regarding the potential use of Trelegy outside the proposed restriction. The PBAC recommended that the current Risk Sharing Arrangement be amended to [REDACTED] for any PBS expenditure beyond these caps and to allow an increase in the subsidisation caps to accommodate the increased patient population proposed in this submission.
- 7.12 The PBAC reiterated its December 2017 recommendation that a DUSC review of Trelegy should be conducted two years after implementation of the expanded listing to explore whether triple therapy market growth has been appropriate.
- 7.13 The PBAC considered that the requested removal of the clinical criteria (FEV1<50% predicted) was also applicable to all ICS/LABA FDC products for COPD on the PBS and as such recommended that flow-on restriction changes to these products were appropriate. The PBAC recommended that the removal of the FEV1 criteria of the COPD indication for all ICS/LABA be accompanied by changes to the clinical criteria to

include specification of exacerbation severity and a 12 month time period for the exacerbation history along with reference to the requirement for a patient to be experiencing significant symptoms despite regular beta-2 agonist therapy. As a result of such changes the PBAC considered that the clinical criterion ‘The treatment must be for symptomatic treatment’ could be removed from the COPD indication for ICS/LABA FDC products. Hence, the PBAC advised the clinical criteria of the COPD indication for ICS/LABA FDC products would include the following two criterion only ‘Patient must have significant symptoms despite regular beta-2 agonist bronchodilator therapy’ AND ‘Patient must have experienced at least one severe COPD exacerbation, which required hospitalisation, or two or more moderate exacerbations in the previous 12 months’. The PBAC considered that, due to the potential for inconsistency with the COPD-X Australian guidelines, the proposed changes to all ICS/LABA FDC products for COPD on the PBS should be included in the PBAC Secretariat correspondence (see in paragraph 7.4) with the organisations responsible for updating the COPD-X guidelines.

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

**Outcome:**

Recommended

## 8 Recommended listing

8.1 Amend existing listing as follows:

Name, Restriction, Manner of administration and form	Max. Qty (packs)	Max Qty (units)	No.of Rpts	Proprietary Name and Manufacturer
FLUTICASONE FUROATE + UMECLIDINIUM + VILANTEROL, Fluticasone furoate 100 microgram/actuation + umeclidinium 62.5 microgram/actuation + vilanterol 25 microgram/actuation powder for inhalation, 30 ACTUATIONS	1	1	5	Trelegy® Ellipta® GSK

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse Practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>PBS Indication:</b>	Chronic Obstructive Pulmonary Disease (COPD)
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency

Public Summary Document – March 2019 PBAC Meeting

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
	<input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p>Patient must have experienced at least one severe COPD exacerbation, which required hospitalisation, or two or more moderate exacerbations in the previous 12 months, with significant symptoms despite regular bronchodilator therapy with a long acting muscarinic antagonist (LAMA) and a long acting beta-2 agonist (LABA) or an inhaled corticosteroid (ICS) and a LABA;</p> <p>OR</p> <p>Patient must have been stabilised on a combination of a LAMA, LABA and an ICS for this condition.</p>
<b>Administrative Advice</b>	<p>Formal assessment and correction of inhaler technique should be performed in accordance with the COPD-X Plan (available at <a href="http://copdx.org.au/">http://copdx.org.au/</a>); the assessment and adherence to correct technique should be documented in the patient's medical records.</p> <p>Diagnosis of COPD should include measurement of airflow obstruction using spirometry, with confirmation of post-bronchodilator airflow obstruction.</p> <p>This product is not PBS-subsidised for the treatment of asthma or the initiation of bronchodilator therapy in COPD.</p> <p>The treatment must not be used in combination with an ICS/LABA, LABA/LAMA or LAMA, LABA or ICS monotherapy.</p> <p>A LAMA includes tiotropium, glycopyrronium, aclidinium or umeclidinium.          A LABA includes olodaterol, indacaterol, salmeterol, formoterol or vilanterol.          An ICS includes fluticasone propionate, fluticasone furoate, budesonide, beclomethasone or ciclesonide.</p> <p>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.</p>

8.2 Amend existing listings for all ICS/LABA FDC products for COPD (Streamlined Authority code 4689) as follows:

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse Practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>PBS Indication:</b>	Chronic Obstructive Pulmonary Disease (COPD)
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p>Patient must have significant symptoms despite regular beta-2 agonist bronchodilator therapy.</p> <p>AND</p> <p>Patient must have experienced at least one severe COPD exacerbation, which required hospitalisation, or two or more moderate exacerbations in the previous 12 months.</p>
<b>Administrative Advice</b>	<p>This product is not indicated for the initiation of bronchodilator therapy in COPD.</p> <p>The treatment must not be used in combination with LABA monotherapy or LAMA/LABA combination therapy.</p> <p>A LAMA/LABA includes acclidinium/formoterol, glycopyrronium/indacaterol, tiotropium/olodaterol, or umeclidinium/vilanterol.</p> <p>Diagnosis of COPD should include measurement of airflow obstruction using spirometry, with confirmation of post-bronchodilator airflow obstruction.</p>

## 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 remove the clinical criteria currently restricting access to Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol) to COPD patients with a forced expiratory volume in one second (FEV1) <50% of predicted.