5.16 UMECLIDINIUM BROMIDE AND VILANTEROL TRIFENATATE, umeclidinium bromide 62.5 microgram/actuation + vilanterol trifenatate 25 microgram/actuation inhalation: powder for, Anoro™ Ellipta®, GlaxoSmithKline Australia Pty Ltd

1 Purpose of Application

1.1 The submission sought a Restricted benefit listing for umeclidinium/vilanterol (UMEC/VI) fixed dose combination for the treatment of chronic obstructive pulmonary disease (COPD) in adults.

2 Requested listing

2.1 **Restricted benefit**
For the treatment of adult patients with chronic obstructive pulmonary disease (COPD) where symptoms persist despite regular bronchodilator treatment with a long acting muscarinic antagonist (LAMA) and/or long acting beta2 agonist (LABA); or
For the treatment of adult patients who have been stabilised on a combination of a LAMA and LABA in separate devices.

2.2 Listing was requested on a cost-minimisation basis with tiotropium plus indacaterol.

2.3 The submission initially sought listing of two strengths of UMEC/VI (62.5/25 microgram and 125/25 microgram). The PBAC noted the advice from the sponsor in its pre-sub-committee response (PSCR) that after discussion with various regulatory agencies, additional data are required to characterise a subpopulation of patients identified as benefiting from the higher strength with regard to lung function and rescue salbutamol use. The sponsor advised in its PSCR that it was no longer requesting listing of UMEC/VI 125/25 on the PBS.

2.4 The PBAC noted that the individual components umeclidinium and vilanterol are not currently available on the PBS.

2.5 The PBAC agreed with the ESC that having a combination product available without having the individual components available was problematic. Patients with COPD cannot be treated in the stepwise manner recommended without changing the LABA and LAMA medications. The PBAC considered there were also risks that patients may transition to combination therapy earlier than clinically necessary due to the individual components being unavailable, or that patients will be prescribed triple therapy with UMEC/VI plus a LABA or LAMA single agent.

3 Background

3.1 The submission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration, the Clinical Evaluation Report and TGA Delegate's Summary were available.

3.2 Umeclidinium/vilanterol FDC powder for inhalation had not previously been considered by the PBAC, nor had the individual components.

4 Clinical place for the proposed therapy

4.1 According to the Australian guidelines for COPD (COPD-X), LABAs and LAMAs are recommended in the treatment algorithm for patients with moderate, severe and very severe COPD, and some patients with mild COPD who may be experiencing high levels of breathlessness. If patients are beginning to experience further exacerbations then a bronchodilator with an inhaled corticosteroid (ICS) is currently recommended.

4.2 The submission proposed that the PBS listing of UMEC/VI will provide an alternative to the only current combination therapy (tiotropium and indacaterol as individual components) available on the PBS. The PBAC agreed with the ESC that due to evidence that inhaled corticosteroid (ICS) use in patients with COPD is associated with an increased risk of pneumonia[1], UMEC/VI may replace some use of ICS/LABA combination therapy. Further, the availability of a LABA/LAMA FDC may lead to patients transitioning to combination therapy earlier than clinically necessary due to the individual components being unavailable.

4.3 The PBAC noted the advice received from the Thoracic Society of Australia and New Zealand (TSANZ) in relation to the use of fixed dose combination LABA/LAMA products in the treatment of COPD. The TSANZ recommended that:

1. Fixed dose LABA/LAMA products will provide improvement in terms of symptomatic breathlessness. However, there is no evidence that they would be superior to the individual agents used concurrently;
2. There is scant data at present to suggest that they are superior to LAMA agents used alone to prevent future events (such as exacerbations and hospitalisations). Further long-term data are still awaited;
3. Given the current practice to prescribe ICS/LABA when stepping up therapy in persistently symptomatic patients from regular LAMA, these agents are likely to provide an effective, convenient and potentially safer alternative. Their availability would promote the current evidence based recommendation of stepwise care and reduce the overuse of ICS in this group.

4.4 The PBAC noted that the treatment algorithm for COPD is changing. The PBAC considered it was appropriate to delay the introduction of ICS/LABA combination therapy in less severe disease, given the potential safety risks associated with ICS use. The PBAC considered that use of the combination of a LAMA and a LABA (as single agents given concurrently or as a fixed dose combination) was preferred to the earlier introduction of an ICS/LABA combination. Such use would be consistent with the Australian COPD-X guidelines, where introduction of an ICS is recommended for

[1] http://www.copdx.org.au/images/stories/pdf/alf%20stepwise%20management%20of%20copd%20a4%202014%20proof.pdf

patients with more severe disease (FEV_1 % predicted <50% predicted and the patient has had two or more exacerbations in the previous 12 months).

5 Comparator

5.1 The submission nominated indacaterol plus tiotropium as the main comparator. The submission also nominated indacaterol/glycopyrronium FDC as a supportive comparator.

5.2 The PBAC considered that the nominated comparators were appropriate.

6 PBAC consideration of the evidence

6.1 The PBAC noted and welcomed the input received from the TSANZ in relation to the clinical place of fixed-dose combination LABA/LAMA products in the treatment of COPD.

6.2 The sponsor did not request a hearing for this item.

Clinical trials

6.3 The submission presented a comparison of UMEC/VI with tiotropium plus indacaterol based on an indirect comparison comprising six randomised trials: DB2113360, DB2113361, DB2113373, DB2113374, $INTRUST_1$, and $INTRUST_2$, using tiotropium as common comparator. The submission presented a primary analysis comprising the integrated results of the four UMEC/VI trials, and a supplementary meta-analysis of the tiotropium controlled UMEC/VI trials. These were compared with INTRUST1 and INTRUST2 trials, which compared tiotropium (18 micrograms) plus indacaterol (150 micrograms) with tiotropium (18 micrograms) plus placebo. Details are presented in the table below.

Trials and associated reports presented in the submission.

Trial ID	Protocol title/ Publication title	Publication citation
Common reference: tiotropium		
UMEC/VI		
DB2113360	A Multicenter Trial Comparing the Efficacy and Safety of GSK573719/GW642444 With GW642444 with Tiotropium Over 24 Weeks in Subjects With COPD	2012
DB2113374	A Multicenter Trial Comparing the Efficacy and Safety of GSK573719/GW642444 With GSK573719 and With Tiotropium Over 24 Weeks in Subjects With Chronic Obstructive Pulmonary Disease (COPD)	2013
Tiotropium + indacaterol		
$INTRUST_1$ & $INTRUST_2$	Concurrent use of indacaterol plus tiotropium in patients with COPD provides superior bronchodilation compared with tiotropium alone: a randomised, double-blind comparison.	Mahler et al *Thorax* (2012); 67: 781-788

Common reference: placebo		
UMEC/VI		
DB2113361	A 24-Week, Randomized, Double-Blind, Placebo-	2012

	Controlled Study to Evaluate the Efficacy and Safety of GSK573719/GW642444 Inhalation Powder and the Individual Components Once-Daily in Subjects With Chronic Obstructive Pulmonary Disease	
DB2113373	A 24-Week, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of GSK573719/GW642444 Inhalation Powder and the Individual Components Once-Daily in Subjects With Chronic Obstructive Pulmonary Disease Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD.	2012 Donohue JF, Maleki-Yazdi MR, Kilbride S, Mehta R, Kalberg C, Church A *Respir Med* (2013); 107(10): 1538-46.

Source: Table 6, p12 of the submission.

6.4 The PBAC considered that the approach used in the commentary, only using data from the tiotropium controlled trials in the meta-analyses, was appropriate. However, the PBAC noted that the use of the different analyses did not have a relevant impact on the results.

6.5 The submission also provided additional indirect comparative analysis of UMEC/VI to indacaterol/glycopyrronium, using tiotropium as the common comparator. Details of the trials are presented in the table below.

Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Indacaterol/glycopyrronium		
SHINE	Dual bronchodilation with glycopyrronium with indacaterol versus single bronchodilator therapy: the SHINE study.	Bateman et al., 2013, ERJ Express. as doi: 10.1183/09031936.00200212
ENLIGHTEN	Safety and efficacy of dual bronchodilation with glycopyrronium with indacaterol in COPD patients: the ENLIGHTEN study.	Dahl et al.,Respiratory Medicine. 2013: (1-10)

Source: Table 6, p12 of the submission. *Sourced during evaluation*

Comparative effectiveness

6.6 All trials reported analysis of trough FEV_1 at 12 weeks, enabling comparison of outcomes at this time point.

6.7 The PBAC noted that it had previously accepted trough FEV_1 as a surrogate measure of effect in COPD. However, the PBAC considered that additional clinical outcomes such as frequency of exacerbations and hospitalisations would be informative as more direct, patient relevant measures of effect.

6.8 The results of the indirect comparison of UMEC/VI vs. indacaterol plus tiotropium, using tiotropium monotherapy as common comparator are presented in the table below. This table also presents the results of the indirect comparisons for the supplementary analyses comparing UMEC/VI with indacaterol/glycopyrronium, using tiotropium as common comparator.

Results of indirect comparison of trough FEV_1 (mL)

	UMEC/VI vs Tio		Comparator(s) vs Tio		Indirect Comparison (95% CI)
	N	LSMD (95% CI)	N	LSMD (95% CI)	
UMEC/VI v indacaterol plus tiotropium (150+18 µg) – 12 Week					
	UMEC/VI vs TIO		**Ind + Tio vs Tio**		
UMEC/VI 62.5/25 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UMEC/VI 125/25 µg	[redacted]	[redacted]			
UMEC/VI v indacaterol/glycopyrronium (110/50 µg) – 24/26 Weeks					
	UMEC/VI vs TIO		**Ind/Gly vs TIO (26 wks)**		
UMEC/VI 62.5/25 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UMEC/VI 125/25 µg	[redacted]	[redacted]			

Source: Table 36, p66 of the submission, additional analysis undertaken during evaluation

[a] Meta-analysis I^2 = 0.0%

[b] Results of single trial (SHINE), no meta-analysis.

LSMD = least square mean difference; TIO = tiotropium; CI = confidence interval; UMEC/VI = umeclidinium/vilanterol. Ind = indacaterol; Gly = glycopyrronium ; wks = weeks

6.9 From the results of the indirect comparison of UMEC/VI versus indacaterol plus tiotropium, the PBAC noted that there was no statistically significant difference in trough FEV_1 at 12 weeks. From the results of the indirect comparison of UMEC/VI versus indacaterol/glycopyrronium, the PBAC noted that UMEC/VI is associated with a greater, but non-statistically significant difference in trough FEV_1 at 24/26 weeks. In each comparison, the 95% confidence intervals were less than the minimal clinically important difference (MCID) of 100 mL.

6.10 The pooled results of trials DB2113360 and DB2113374 (the tiotropium controlled trials) showed a difference in trough FEV_1 at 12 weeks of [redacted]mL (95% CI: [redacted]) for UMEC/VI 62.5/25 micrograms compared to tiotropium monotherapy. The PBAC noted that while this was a statistically significant increase in FEV_1, this difference did not exceed the accepted MCID of 100-140mL.

6.11 The PBAC considered that there was biological plausibility for a ceiling effect of combination therapy on FEV_1. The PBAC therefore considered that it might be reasonable to accept that the same MCID should not apply to add-on therapy, and the effect of add-on therapy in terms of frequency of exacerbations may be a more patient relevant measure of effect.

6.12 The PBAC was unable to assess the comparative efficacy of UMEC/VI FDC and the component therapies given concurrently. The PBAC considered it would have been preferable to assess the components umeclidinium and vilanterol individually before undertaking an assessment of the FDC.

Comparative harms

6.13 A summary of adverse events observed in the included trials is presented in the tables below.

Summary of key adverse events in the randomised trials

Trial	Intervention (mcg)		Control	Relative Risk	
DB2113360 (24 weeks)	**UMEC/VI 62.5/25**	**UMEC/VI 125/25**	**TIO 18 mcg**	**UMEC/VI 62.5/25 vs TIO**	**UMEC/VI 125/25 vs TIO**
n	212	214	208		
AEs	114 (54%)	99 (46%)	84 (40%)	**1.3 (1.0, 1.6)**	1.1 (0.9, 1.4)
SAEs	9 (4%)	7 (3%)	13 (6%)	0.7 (0.3, 1.6)	0.5 (0.2, 1.3)
Discont due to AE	10 (5%)	15 (7%)	9 (4%)	1.09 (0.45, 2.63)	1.62 (0.72,3.62)

Trial	**Intervention (mcg)**		**Control**	**Relative Risk**	
Death	1 (<1%)	0 (0%)	0 (0%)		
DB2113374 (24 weeks)	**UMEC/VI 62.5/25**	**UMEC/VI 125/25**	**TIO 18 mcg**	**UMEC/VI 62.5/25 vs TIO**	**UMEC/VI 125/25 vs TIO**
n	217	215	215		
AEs	130 (60%)	141 (66%)	129 (60%)	1.0 (0.9, 1.2)	1.1 (0.9, 1.2)
SAEs	23 (11%)	17 (8%)	9 (4%)	**2.5 (1.2, 5.3)**	1.9 (0.9, 4.1)
Discont due to AE	20 (9%)	15 (7%)	11 (5%)	1.8 (0.9, 3.7)	1.4 (0.6, 2.9)
Death	1 (<1%)	1 (<1%)	2 (1%)	0.5 (0, 5.4)	0.5 (0, 5.5)
INTRUST $_1$ (12 weeks)	**Ind+TIO 110+18**		**TIO 18 mcg**	**Ind+TIO vs TIO 110+18 vs 18 mcg**	
n	570		561		
AEs	259 (45%)		231 (41%)	**1.1 (1, 1.3)**	
SAEs	21 (4%)		17 (3%)	1.2 (0.6, 2.3)	
Discont due to AE	NR		NR	NR	
Death	2 (<1%)		0 (0%)	NC	
INTRUST $_2$ (12 weeks)	**Ind+TIO 150+18**		**TIO**	**IND+TIO vs TIO 150+18 vs 18 mcg**	
n	572		570		
AEs	246 (43%)		229 (40%)	1.1 (0.9, 1.2)	
SAEs	19 (3%)		18 (3%)	1.1 (0.6, 2)	
Discont due to AE	NR		NR	NR	
Death	1 (<1%)		2 (0%)	0.5 (0, 5.5)	
SHINE (52 weeks)	**Ind/Gly 110/50**		**TIO**	**Ind/Gly vs TIO 110/50 vs 18 mcg**	
n	474		480		
AEs	261 (55%)		275 (57%)	1.0 (0.9, 1.1)	
SAEs	22 (5%)		19 (4%)	1.2 (0.6, 2.1)	
Discont due to AE	9 (2%)		15 (3%)	0.6 (0.3, 1.4)	
Death	1 (<1%)		3 (1%)	0.3 (0, 3.2)	

Extracted and calculated during evaluation from UMEC/VI trial CSRs provided with the submission, Dahl et al 2013, Bateman et al 2013, Mahler et al 2012.
UMEC/VI = umeclidinium/vilanterol; TIO = tiotropium; IND = indacaterol; GLY = glycopyrronium; n = patients in trial arm; AEC = adverse event(s); NR = not reported; Discont = discontinued; NC = not calculable

6.14 In the UMEC/VI trials, there was a statistically significantly higher number of patients reporting an adverse event (DB2113360) or serious adverse event (DB2113374) from UMEC/VI 62.5/25 microgram combination therapy. DB2113374 reported twice the proportion of serious adverse events in its intervention arms compared to the other included randomised trials. A statistically significant number of patients reporting an adverse event were also identified in the INTRUST$_1$ trial.

6.15 The submission identified that the UMEC/VI trials had a slightly higher incidence of adverse events compared with the INTRUST trials. It suggested that this may be attributable to the longer treatment duration of the UMEC/VI trials (24 weeks vs. 12 weeks treatment in the INTRUST trials). It argued that overall safety results were generally consistent between trials and that the agents have a similar safety profile.

Harm summary – meta analyses

Outcome	N	RR (95%CI)	Event rate/100 patients		
UMEC/VI 62.5/25 µg vs. TIO 18 µg 24 Weeks (meta-analysis, n=2)			**UMEC/VI 62.5/25 µg**	**TIO 18 µg**	**Increment**
Drug related AEs	852	1.1 (0.9, 1.5)	54.8	49.2	5.6
Disc due to AE	852	1.1 (0.4, 3)	7.0	6.1	0.9
Drug related SAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UMEC/VI 125/25 µg vs. TIO 18 µg 24 Weeks (meta-analysis, n=2)			**UMEC/VI 125/25 µg**	**TIO 18 µg**	**Increment**
Drug related AEs	852	1.1 (0.9, 1.2)	52.9	49.2	3.7
Disc due to AE	852	0.9 (0.5, 2)	5.8	6.1	-0.3
Drug related SAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IND+TIO 150+18 µg vs. TIO 18 µg 12 Weeks (meta-analysis, n=2)			**IND+TIO 150+18 µg**	**TIO 18 µg**	**Increment**
Drug related AEs	2273	1.1 (1, 1.2)	44.2	40.7	3.5
Disc due to AE	2273	NR	NR	NR	-
Drug related SAE	2273	1.1 (0.7, 1.8)	3.5	3.1	0.4
IND/GLY 110/50 µg vs. TIO 18 µg 52 Weeks (n=1)			**IND/GLY 110/50 µg**	**TIO 18 µg**	**Increment**
Drug related AEs	954	1 (0.9, 1.1)	55.1	57.3	-2.2
Disc due to AE	954	0.6 (0.3, 1.4)	1.9	3.1	-1.2
Drug related SAE	954	1.2 (0.6, 2.1)	4.6	4.0	0.6

Source: Table 3 p4 of the commentary.
UMEC/VI = umeclidinium/vilanterol; TIO = tiotropium; IND = indacaterol; GLY = glycopyrronium; N = patients; n = number of studies AE = adverse event(s); SAE = serious adverse events; Disc = discontinuation; NR = not reported

6.16 The PBAC noted that based on the trials presented, for every 100 patients treated with UMEC/VI (62.5/25 micrograms) compared to tiotropium, approximately six patients would experience a drug related adverse event, there would be one discontinuation due to adverse events, and two patients would experience a drug related serious adverse event.

6.17 An indirect treatment comparison of the comparative safety of UMEC/VI 62.5/25 micrograms to indacaterol 150 micrograms plus tiotropium 18 micrograms was provided in the sponsor's PSCR (p2). Details are presented in the table below.

Indirect treatment comparison of the comparative safety of UMEC/VI 62.5/25 mcg to IND 150 + TIO 18 mcg

[redacted]

6.18 The sponsor stated that the results suggest that all on-treatment AEs, SAEs and fatal AEs for UMEC/VI 62.5/25 mcg and indacaterol plus tiotropium are similar, with no significant differences.

6.19 Common adverse events across the UMEC/VI trials were headache, nasopharyngitis, upper respiratory tract infection, and cough. Common serious adverse events included COPD exacerbations and pneumonia. In DB2113374 there was a significantly higher relative risk of serious adverse events for the UMEC/VI 62.5/25

trial arm. This was related to a higher proportion of reported respiratory tract infections in these patients. The indacaterol plus tiotropium and indacaterol/glycopyrronium trials reported similar adverse events to the UMEC/VI trials.

6.20 The PBAC noted that a safety issue not measured in the trials was the potential for patients to be prescribed a higher than recommended dose of LABA and/or LAMA. A predicted versus actual utilisation review of indacaterol conducted by the Drug Utilisation Sub Committee (DUSC) highlighted the potential for confusion and incorrect dosing of FDC products. The DUSC analysis showed that 20.8% of patients who initiated indacaterol between December 2011 and November 2012 were also taking, and continued to take, an ICS/LABA concomitantly (i.e. these patients added indacaterol to an ICS/LABA); there is no clinical evidence to support the safety or efficacy of using two LABAs. The PBAC agreed with the ESC that the introduction of a LABA/LAMA FDC could further increase the risk of incorrect or double-dosing of products for COPD. The PBAC also considered there is a risk that patients with concomitant asthma may be co-prescribed LAMA/LABA FDC and an ICS/LABA FDC. The use of inappropriately high doses of LABA (or LAMA) would lead to an unknown but likely increased risk of harm.

6.21 In the Guidelines for Preparing Submissions to the PBAC, the section dealing with FDC products notes that it is preferable that the components of the FDC are also listed on the PBS. The PBAC particularly noted that although clinical experience with LABAs as a class is extensive, vilanterol is a new agent. Similarly, while there is substantial clinical experience with tiotropium, umeclidinium is a new LAMA.

Clinical claim

6.22 The submission claimed that UMEC/VI combination therapy has comparable effectiveness to indacaterol (150 µg) plus tiotropium (18 µg) at 12 weeks. The submission also claimed that UMEC/VI combination therapy is non-inferior in terms of efficacy to indacaterol/glycopyrronium (110/50 micrograms).

6.23 The submission claimed that UMEC/VI combination therapy has a mostly benign and similar safety profile to indacaterol plus tiotropium, and is non-inferior in terms of safety to indacaterol/glycopyrronium.

6.24 The PBAC considered the submission's claims with regard to efficacy were reasonable for trough FEV_1, with the limitation that the claims are based on indirect comparisons.

6.25 The PBAC considered that the submission's claims with regard to comparative safety may not be reasonable. The PBAC noted that there was a slight increase in adverse event rates for UMEC/VI in the presented trial data.

Economic analysis

6.26 The submission presented a cost-minimisation analysis based on the non-inferiority claim versus tiotropium plus indacaterol. The equi-effective doses were estimated as UMEC/VI 62.5/25 micrograms and tiotropium 18 micrograms plus indacaterol 150 micrograms. A summary of the cost-minimisation analysis is presented in the table below.

Cost minimisation analysis – UMEC/VI versus tiotropium + indacaterol

Molecule	Packs	DPMQ	PTP	*Ex-man*
Comparator				
Indacaterol 150 µg	[redacted]	[redacted]	[redacted]	[redacted]
Tiotropium 18 µg	[redacted]	[redacted]	[redacted]	[redacted]
Open combination Ind + Tio 150+18 µg	[redacted]	[redacted]	[redacted]	[redacted]
UMEC/VI				
UMEC/VI 62.5/25 µg	[redacted]	[redacted]	[redacted]	[redacted]

Source: Tables 62-63, p102 of the submission.
UMEC/VI = umeclidinium/vilanterol; Ind = indacaterol; Tio = tiotropium

[redacted]

6.27 Based on the clinical evidence provided in the submission, the equi-effective doses for the comparison with indacaterol/glycopyrronium were determined to be UMEC/VI 62.5/25 micrograms and indacaterol/glycopyrronium 110/50 micrograms. Details of the cost-minimisation analysis for this comparison are presented in the table below.

Cost minimisation analysis – UMEC/VI versus indacaterol/glycopyrronium

Molecule	Ex-man	Proportion based on dosing	Price per µg	Requested price
Indacaterol 150 µg	[redacted]	[redacted]	[redacted]	[redacted]
Glycopyrronium 50 µg	[redacted]	[redacted]	[redacted]	[redacted]
Ex-manufacturer				[redacted]
Price to pharmacist				[redacted]
DPMQ				[redacted]

Source: Table 158 & Table 159, p279 of the submission;
Ex-man = ex –manufacturer

6.28 The PBAC noted that the incremental gain in FEV_1 of UMEC/VI compared to tiotropium monotherapy is [redacted] mL (95% CI: [redacted], [redacted]) at 12 weeks. The PBAC considered that the submission's proposal to price the FDC based on the sum of the prices of indacaterol plus tiotropium, while consistent with the PBAC Guidelines for combination products, could not be justified given that the price would be approximately twice that of tiotropium despite the submission not having presented evidence to demonstrate an incremental benefit of this magnitude. In this situation, the PBAC considered it would be appropriate for the price of UMEC/VI to be based on the value of the incremental gain in clinically relevant efficacy endpoints.

6.29 As the incremental gain in FEV_1 of UMEC/VI was not able to be translated into more clinically relevant measures of effect (e.g., frequency of exacerbations, hospitalisations), the PBAC considered it was unable to determine and value the incremental benefit associated with use the UMEC/VI compared with use of tiotropium plus indacaterol given concurrently. Therefore, the Committee was unable to determine an appropriate price for the FDC.

Estimated PBS usage & financial implications

6.30 The submission used a combined epidemiological and market share approach to estimate the utilisation and financial implications associated with the requested listing. Details are presented in the table below.

Projected patients and prescriptions for UMEC/VI

	Year 1[a]	Year 2	Year 3	Year 4	Year 5
Estimated extent of use – UMEC/VI					
UMEC/VI market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients treated with UMEC/VI [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prescriptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated cost to PBS/RPBS – UMEC/VI					
PBS/RPBS cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Co-payment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total PBS/RPBS cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated changes in use and cost of tiotropium plus indacaterol					
Reduction patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prescriptions offset [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Copayment [c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost of listing UMEC/VI					
Cost of UMEC/VI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of Tio + Ind	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.31 The likely number of patients per year was estimated in the submission to be between 10,000 and 50,000 in Year 5, at an estimated net cost per year to the PBS of less than $10 million in Year 5.

6.32 The PBAC agreed with the DUSC that the estimates presented in the submission were significantly underestimated based on the following:

- The current dual therapy LAMA plus LABA market may have been overestimated by including LABA monotherapy patients, but the projected LAMA plus LAMA market may be underestimated.
- By considering LAMA plus LABA only, and excluding ICS, the total substitutable market was significantly underestimated. This has significant implications throughout the estimates.
- The estimates relied on a sample of PBS data for which the specific methodology was not provided in the submission. The DUSC was therefore unable to verify a number of steps used to derive the estimates. (The PBAC noted that the sponsor provided this information with its pre-PBAC response).

6.33 The PBAC shared the DUSC's concerns in relation to the trade names and proliferation of inhalers being confusing for prescribers and patients. The PBAC agreed that a quality use of medicines (QUM) issue exists where this potential confusion may lead to use of multiple LAMAs or LABAs and associated clinical consequences.

6.34 The PBAC also noted newly emerging data that shows there may be a role for LAMAs in asthma, when used in conjunction with and ICS +/- LABA, although this has not yet been fully determined[2].

[2] Lipworth B. Emerging role of long acting muscarinic antagonists for asthma. Br J Clin Pharmacol 2014; 77(1):55–62.

7 PBAC Outcome

7.1 The PBAC rejected the submission requesting PBS-listing for UMEC/VI FDC for the treatment of COPD. The PBAC considered that the cost-minimisation approach used, where the price of the FDC was cost-minimised to the sum of the prices of indacaterol plus tiotropium was not justified by the evidence presented in the submission.

7.2 The PBAC also considered that having a combination product available without having the individual components available was problematic. Patients with COPD cannot be treated in the stepwise manner recommended without changing the LABA and LAMA medications. The PBAC considered there were also risks that patients may transition to combination therapy earlier than clinically necessary due to the individual components being unavailable, or that patients will be prescribed triple therapy with UMEC/VI plus a LABA or LAMA single agent.

7.3 The PBAC was unable to assess the comparative efficacy of UMEC/VI FDC and the component therapies given concurrently. The PBAC advised that it would have been preferable to assess the components umeclidinium and vilanterol individually before undertaking an assessment of the FDC.

7.4 The PBAC considered that the submission's nominated comparators were appropriate.

7.5 The PBAC considered the submission's claims that UMEC/VI combination therapy has comparable effectiveness to indacaterol (150 µg) plus tiotropium (18 µg) at 12 weeks, and that that UMEC/VI combination therapy is non-inferior in terms of efficacy to indacaterol/glycopyrronium (110/50 micrograms), were reasonable based on the evidence presented for FEV_1.

7.6 The PBAC considered that the submission's claims with regard to comparative safety may not be reasonable. The PBAC noted that there was a slight increase in adverse event rates for UMEC/VI in the presented trial data.

7.7 The PBAC noted that the incremental gain in FEV_1 of UMEC/VI compared to tiotropium monotherapy is [redacted]mL (95% CI: [redacted], [redacted]) at 12 weeks. The PBAC considered that the submission's proposal to price the FDC based on the sum of the prices of indacaterol plus tiotropium, while consistent with the PBAC Guidelines for combination products, could not be justified given that the price would be approximately twice that of tiotropium despite the submission not having presented evidence to demonstrate an incremental benefit of this magnitude. In this situation, the PBAC considered it would be appropriate for the price of UMEC/VI to be based on the value of the incremental gain in other clinically relevant efficacy endpoints.

7.8 However, as the incremental gain in FEV_1 of UMEC/VI was not able to be translated into more clinically relevant measures of effect (e.g., frequency of exacerbations, hospitalisations), the PBAC was unable to determine and value the incremental benefit associated with use the UMEC/VI compared with use of tiotropium plus

indacaterol given concurrently. Therefore, the Committee was unable to determine an appropriate price for the FDC.

7.9 The PBAC did not accept the estimates of utilisation presented in the submission. The PBAC agreed with the DUSC that the total substitutable market was underestimated. The PBAC agreed that it was possible that patients may switch from ICS/LABA to LAMA/LAMA regardless of the treatment algorithm, due to the availability of new LAMA/LABA combination products. The PBAC considered that as a consequence of advice in the most recent GOLD guidelines[3] in relation to risks associated with long-term use of inhaled corticosteroids (pneumonia and increased fracture risk) that it was possible that there would be delayed movement of COPD patients to treatment with ICS/LABA, which would result in expanded use of LAMA/LABA. The PBAC considered that the advice received from the TSANZ supported this view.

7.10 The PBAC considered that should UMEC/VI be recommended for PBS listing in the future, a risk-sharing arrangement would be required to manage the risk associated with higher than estimated usage and cost.

7.11 The PBAC again raised its concerns in relation to the trade names and proliferation of inhalers for treatment of COPD being confusing for prescribers and patients. The PBAC agreed that a quality use of medicines (QUM) issue exists where this potential confusion may lead to use of multiple LAMAs or LABAs and associated clinical consequences. The PBAC referred the matter of QUM of COPD treatments to NPS MedicineWise and requested they produce information and education for prescribers in relation to this.

7.12 The PBAC noted that the submission meets the criteria for an Independent Review.

Outcome:
Rejected

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.

Sponsor's Comment
GlaxoSmithKline is disappointed by the decision but will continue to work with the PBAC to make Anoro available for Australian COPD patients.

In relation to 6.13, in the Table 'Summary of key adverse events in the randomised trials', the Sponsor would like to clarify that AEs and SAEs relevant to the UMEC/VI trials DB2113360 & DB2113374 refer to on and post treatment adverse events.

In relation to 6.19, common AEs refer to those occurring in ≥3% of patients in any treatment group. Common SAEs refer to those occurring in ≥1% of patients in any treatment group. In terms of the SAE pneumonia, the Sponsor would like to note that there were no pneumonia associated SAEs reported in trial DB2113360, while in DB2113374 there were only 2

[3] From the Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2013. Available from: http://www.goldcopd.org/.

pneumonia related events reported in both the UMEC/VI 62.5/25 mcg and TIO 18 mcg treatments arms (<1%).