5.7 FLUTICASONE FUROATE AND VILANTEROL TRIFENATATE, dry powder inhaler, fluticasone furoate 100 microgram/actuation + vilanterol trifenatate 25 microgram/actuation, Breo® Ellipta®, GlaxoSmithKline Australia Pty Ltd.

1 Purpose of Application

1.1 The submission sought a Restricted Benefit listing for fluticasone furoate/vilanterol (FF/VI) fixed dose combination (FDC) 100/25 micrograms for the treatment of chronic obstructive pulmonary disease (COPD).

2 Requested listing

2.1 **Restricted benefit**
Symptomatic treatment of COPD, where the FEV_1 is less than 50% predicted normal and there is a history of repeated exacerbation with significant symptoms despite regular beta-2 agonist bronchodilator therapy.

2.2 Listing was sought on a cost-minimisation basis compared with fluticasone propionate/salmeterol fixed dose combination using a claim of non-inferiority.

2.3 The PBAC considered that should FF/VI be recommended for listing, a note should be incorporated into the restriction specifying that the patient must not be on a concomitant single agent LABA.

2.4 The PBAC noted that the individual components fluticasone furoate and vilanterol are not currently available on the PBS. The PBAC noted that fluticasone (as propionate) is available on the PBS in various strengths and in various inhalation devices as an unrestricted benefit.

3 Background

3.1 The submission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration, the Clinical Evaluation Report, TGA Delegate's Summary and ACPM outcome were available. At the time of PBAC consideration, FF/VI FDC powder for inhalation was not yet TGA registered for the treatment of COPD.

3.2 At its December 2013 meeting, the Advisory Committee on Prescription Medicines (ACPM) considered FF/VI to have an overall positive benefit-risk profile for the following amended indication for COPD:

"Symptomatic treatment of patients with COPD with a FEV1< 70% predicted and a history of exacerbations despite regular bronchodilator therapy.

BREO ELLIPTA is not indicated for the initiation of bronchodilator therapy in COPD"

3.3 FF/VI FDC powder for inhalation had not previously been considered by the PBAC. Nor had the individual components been previously considered.

4 Clinical place for the proposed therapy

4.1 According to the Australian guidelines for COPD (COPD-X), ICS plus LABA is recommended in the treatment algorithm for patients with COPD where FEV_1 is <50% predicted and the patient has had two or more exacerbations in the previous 12 months.

4.2 The submission proposed that FF/VI will be used in patients with a FEV_1<50% predicted normal and history of repeated exacerbations, which aligns with the existing PBS restriction for other ICS/LABA FDCs in COPD. The PBAC noted that the requested restriction was narrower than the proposed TGA indication. The proposed TGA indication allows use in symptomatic treatment of patients with COPD with a FEV_1 <70% predicted normal and a history of exacerbations despite regular bronchodilator therapy.

4.3 The PBAC noted the advice received from the Thoracic Society of Australia and New Zealand (TSANZ). This advice expressed concerns that prescribers may be commencing COPD patients on ICS/LABA FDCs rather than single-agent LABA (or LAMA). TSANZ noted that this is not recommended by the COPD-X guidelines, which recommend limiting combination ICS/LABA in COPD only to those patients with moderate to severe disease or frequent exacerbations. The TSANZ further stated that 'the widespread use of ICS would therefore also expose patients potentially to the side effects of these agents, with concerns remaining in regard to high dose inhaled corticosteroid use, specifically a heightened risk of pneumonia."

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 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 patients with more severe disease (FEV_1 % predicted <50% predicted and the patient has had two or more exacerbations in the previous 12 months[1]).

4.5 The submission proposed that FF/VI will predominantly replace fluticasone propionate/salmeterol (FP/SAL) and, to a lesser degree, budesonide/eformoterol (BUD/FOR).

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

4.6 The PBAC noted that FF/VI is administered once daily, unlike the other ICS/LABA FDCs that are currently listed which are recommended to be administered twice daily.

5 Comparator

5.1 The submission nominated FP/SAL 500/50 FDC as the main comparator, and BUD/FOR 400/12 FDC as a secondary comparator.

5.2 The PBAC considered that the nominated comparators were appropriate.

6 PBAC consideration of the evidence

Consumer comments and sponsor hearing

6.1 The sponsor did not request a hearing.

6.2 The PBAC noted that a letter was received from the Thoracic Society of Australia and New Zealand (TSANZ). This advice discussed the place in therapy of ICS/LABA FDCs in COPD (refer to paragraph 4.3).

Clinical trials

6.3 The submission was based on one head-to-head randomised trial comparing FF/VI 100/25 once daily to FP/SAL 500/50 twice daily (Trial HZC113107).

6.4 Details of the trial are shown in the table below.

Trials and associated reports presented in the submission

Trial	Protocol title/ Publication title	Publication citation
Direct randomised trial		
HZC113107	A Randomised, Double-Blind, Double Dummy, Parallel Group, Multi-centre Study to assess efficacy and safety of FF/VI 100/25 mcg inhalation powder and FP/SAL inhalation powder on lung function in subjects with COPD	October 2011 *Eur Respir J* 2013, October 10 Published online before print as doi: 10.1183/09031936.00054213

Abbreviations: FF/VI = Fluticasone Furoate/Vilanterol, FP/SAL = Fluticasone Propionate/Salmeterol, COPD = Chronic Obstructive Pulmonary Disease

Comparative effectiveness

6.5 The primary outcome in trial HZC113701 was change from baseline trough in 24-hour weighted mean serial FEV_1 at the end of 12 weeks of treatment. Quality of life (QoL) determined using St George's Respiratory Questionnaire – COPD (SGRQ-C), and health status using the EQ-5D were secondary outcomes. The results of Trial HZC113107 are presented in the table below.

6.6 Trial HZC113107 was conducted in COPD patients who had a post salbutamol FEV_1 <70% of predicted normal. The submission also presented a subgroup analysis of patients with a post-salbutamol FEV_1 of <50% of predicted normal, which was consistent with the requested PBS restriction.

Results of Trial HZC113107

Population	Fluticasone Furoate 100mcg+ vilanterol 25 mcg OD	Fluticasone Propionate 500mcg + salmeterol 50mcg BD	Mean difference (95%CI)
Weighted mean serial FEV 0-24 h on day 84, LS mean change (SE)			
ITT	n/N = 224/266 0.130 (0.015)	n/N = 233/262 0.108 (0.015)	0.022 (-0.018, 0.063)
ITT, FEV_1 <50% predicted normal	[redacted]	[redacted]	[redacted]
Change from baseline in trough FEV_1, mean change (SE)			
ITT	n/N = 242/266 0.111 (0.016)	n/N = 245/262 0.088 (0.015)	0.023 (-0.020, 0.066)
ITT, FEV_1 <50% predicted normal*	[redacted]	[redacted]	[redacted]
Change in baseline SGRQ-C total score to day 84, LS mean change (SE)			
ITT	n/N=236/266 -4.78 (0.86)	n/N = 242/262 -3.29 (0.84)	-1.50 (-3.86, 0.87)
ITT, FEV_1 <50% predicted normal	[redacted]	[redacted]	[redacted]
Change in baseline EQ-5D values at day 84, LS mean change (SE)			
ITT	n/N = 243/266 0.02 (0.01)	n/N = 246/262 0.02 (0.01)	-0.002 (-0.04, 0.03)
ITT, FEV_1 <50% predicted normal	[redacted]	[redacted]	[redacted]

*This comparison was conducted *post hoc*

Abbreviations: ITT = Intention to Treat; LS = least squares, SE = standard error, SGRQ-C = St. George's Respiratory Questionnaire – COPD, EQ-5D = EuroQOL questionnaire

Source: Table 28, p69, Table 29, p71, Table 30 and 31, p72, Table 32, p74, Table 35, p77, Table 36, p78, Table 37 and 38, p79 of the submission

6.7 The PBAC considered that, based on the non-inferiority margin of 100mL–140 mL for FEV_1 measurements, the results of Trial HZC113107 supported a non-inferiority claim between FF/VI 100/25 once daily and FP/SAL 500/50 twice daily in both the Intention to Treat (ITT) population and in patients with baseline FEV_1 <50% predicted normal (the population most representative of those for whom listing is sought). A non-inferiority claim would also be supported using the Minimal Clinically Important Difference (MCID) of 60mL which was used in Trial HZC113107 as the superiority margin.

6.8 The PBAC considered that trough FEV_1 was a clinically relevant outcome for benefits and recalled it had been previously accepted this as a surrogate measure. 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.

6.9 With regard to the QoL measures, there were no statistically significant differences between the two treatment groups in either SGRQ-C or EQ-5D in trial HZC113107.

6.10 The PBAC noted that the trial participants had to be over 40 years of age and had to be a current or former smoker. The PBAC considered that this may affect the applicability of the trial results to the proposed PBS population.

Comparative harms

6.11 A summary of adverse events observed in Trial HZC113107 is presented in the table below.

Summary of key adverse events in Trial HZC113107

Adverse events	**FF/VI (N= 266) n (%)**	**FP/SAL (N=262) n (%)**	**RR (95% CI)**
Any adverse event	73 (27.4)	68 (26.0)	*1.06 (0.80, 1.40)*
Adverse event leading to discontinuation or withdrawal	6 (2.3)	3 (1.1)	*1.97 (0.50, 7.80)*
Non-Fatal serious adverse event	6 (2.3)	3 (1.1)	*1.97 (0.50, 7.80)*
Drug related adverse events	4 (1.5)	9 (3.4)	*0.44 (0.14, 1.40)*
Adverse events of special interest			
Cardiovascular events	9 (3.4)	1 (0.4)	***8.87 (1.13, 69.48)***
Local steroid effects	3 (1.1)	10 (3.8)	*0.30 (0.08, 1.06)*
Oral candidiasis	2 (0.8)	4 (1.5)	*0.49 (0.09, 2.67)*
Orophargyngeal candidiasis	0	3 (1.1)	*0.14 (0.01, 2.71)*
Oropharyngeal pain	0	3 (1.1)	*0.14 (0.01, 2.71)*
Hypersensitivity	2 (0.8)	2 (0.8)	*0.99 (0.14, 6.94)*
LRTI excluding pneumonia	2 (0.8)	0	*4.93 (0.24, 102.10)*
Pneumonia	1 (0.4)	2 (0.8)	*0.49 (0.05, 5.40)*
Systemic steroid events	0	0	*NA*

Text in bold indicates statistical significant differences
Source: Table B.6.3 p21 of the commentary

6.12 The PBAC noted that there was a statistically significant difference in the incidence of cardiovascular events between patients treated with FF/VI and patients treated with FP/SAL (RR 8.87 [1.13, 69.48] in Trial HZC113107.

6.13 The PBAC agreed with the ESC that despite the small number of events (nine in the FF/VI arm and one in the FP/SAL arm), the cardiovascular risk associated with FF/VI in patients with COPD is a significant comparative safety concern.

6.14 The PBAC noted that apart from cardiovascular events, there was no evidence of any safety issues with FF/VI compared with FP/SAL within Trial HZC113107.

6.15 The PBAC noted that the short duration of Trial HZC113107 (12 weeks) limited the information available to inform the longer term comparative safety of FF/VI, particularly in terms of the risk of cardiovascular events and pneumonia.

6.16 The submission provided pooled results of the pneumonia risk across all ten FF/VI COPD integrated studies (ITT population), and found the rate of pneumonia was [redacted]/1000 treatment years with FF/VI 100/25 compared to [redacted]/1000 treatment years with FF100 alone, [redacted]/1000 treatment years with FP/SAL 500/50 and [redacted]/1000 with placebo.

Summary of on-treatment pneumonia in COPD (All FF/VI 10 Studies ITT Population)

	Placebo N=584	FF/VI 50/25 N=1060	FF/VI 100/25 N=2034	FF/VI 200/25 N=1047	VI 25 N=1327	FF 100 N=410	FF 200 N=203	FP/SAL 250/50 N=511	FP/SAL 500/50 N=262
Subjects with Pneumonia									
n (%)	[redacted]								
Per 1000 treatment years									
Number of events									
Event rate/1000 treatment years									
Subjects with Severe Pneumonia									
n (%)	[redacted]								
Per 1000 treatment years									
Number of events									
Event rate/1000 treatment years									
Subjects with Serious Pneumonia									
n (%)	[redacted]								
Per 1000 treatment years									
Number of events									
Event rate/1000 treatment years									
Subjects with Fatal Pneumonia									
n (%)	[redacted]								
Per 1000 treatment years									
Number of events									
Event rate/1000 treatment years									

Source: Table 58 p99 of the submission

ITT = Intention to Treat; FF = fluticasone furoate; VI = vilanterol; FP/SAL = fluticasone propionate/salmeterol

6.17 The PBAC noted a recent analysis based on a population-based cohort of over 160,000 patients with COPD followed for up to 18 years using the Quebec health insurance database.[2] The authors found that current use of ICS was associated with a 69% increase in the rate of serious pneumonia (RR 1.69, 95% CI 1.63 to 1.75). The risk was sustained with long-term ICS use and declined gradually after ceasing ICS therapy. The PBAC noted that the rate of serious pneumonia was higher with fluticasone (salt not specified in the publication) than budesonide, with the rate ratio increasing proportionally to the daily dose.

6.18 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. 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 considered that the introduction of another ICS/LABA FDC could further increase the risk of confusion and incorrect and double-dosing. The use of inappropriately high doses of LABA would lead to an unknown but likely increased risk of harm.

Clinical claim

6.19 The submission claimed that FF/VI 100/25 FDC is non-inferior in terms of comparative effectiveness and comparative safety over the FP/SAL 500/50 FDC in the treatment of COPD.

6.20 The PBAC considered the submission's claim with regard to comparative effectiveness was reasonable.

6.21 The PBAC considered the submission's claim with regard to comparative safety was not justified by the existing evidence. The PBAC noted the increased rate of cardiovascular events in the 12 week pivotal trial, and the risk of pneumonia associated with ICS use in COPD. Therefore, the PBAC did not accept the submission's claim that FF/VI 100/25 is non-inferior in terms of safety compared to FP/SAL 500/50.

Economic analysis

6.22 The submission presented a cost-minimisation analysis based on a non-inferiority claim versus FP/SAL 500/50mcg FDC.

6.23 The equi-effective doses were estimated as FF/VI 100/25mcg once daily and FP/SAL 500/50mcg twice daily The PBAC noted that this was different to the dose equivalence proposed in the submission for this product for the indication of asthma, which used equi-effective doses of FF/VI 100/25mcg and FP/SAL 250/50mcg.

6.24 A summary of the cost-minimisation analysis that was presented in the submission is shown in the table below.

[2] Suissa S et al. Inhaled Corticosteroids in COPD and the risk of serious pneumonia. Thorax 2013;68:1029-36.

Cost-minimisation analysis of FF/VI to FP/SAL – based on COPD price only

Product	PBS Code	Strength (mcg)	Max Qty	Pack size	*PTP*	DPMQ
FF/VI 100/25						
FP/SAL *(COPD price)*	8432T	500/50	1	60	*$60.93*	$73.65[a]
FF/VI (COPD only)	N/A	100/25	1	30	*$60.93*	$73.65

[a] cost minimised against FP/SAL 500/50 for COPD, which is cost minimised against tiotropium. (DPMQ $73.65). PTP=Price to pharmacist

6.25 The PBAC noted the sponsor's pre-PBAC offer of a lower price for this indication.

6.26 The PBAC considered that, based on the evidence presented in the submission, the equi-effective doses proposed were reasonable.

6.27 The sponsor had proposed a weighted price between the asthma and COPD indications for FF/VI 100/25 of [redacted]% and [redacted]% respectively, based on PBS utilisation data. The PBAC noted that this is different to the weighting in asthma and COPD that is currently used in the price for FP/SAL ([redacted]% and [redacted]% respectively).

Estimated PBS usage & financial implications

6.28 The submission used a market share approach to estimate the financial implications of listing FF/VI on the PBS. Details are presented in the table below.

6.29 The PBAC noted that the [redacted]% price reduction offered by the sponsor would increase the saving.

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use FF/VI 100/25					
Utilisation number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS/RPBS/MBS (COPD only)					
Net cost to PBS[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to MBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost Offsets[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assume growth rate is 6.7% (2008-2009) instead of 10.3% (2011-2012, base case)					
Net cost to PBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost Offsets	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assume growth rate is 4.1% (200-2010) instead of 10.3% (2011-2012, base case)					
Net cost to PBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost Offsets	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated total net cost (Asthma + COPD)					
Net Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Adjusted for an average co-payment of $14.66 per dispensing

6.30 The likely number of packs dispensed per year was estimated in the submission to be 10,000 to 50,000 in Year 5, at an estimated net saving per year to the PBS of less than $10 million in Year 5.

6.31 The PBAC considered that the submission's estimate of the growth rate for ICS/LABAs in COPD (10.3% annual growth) may be an overestimate if clinical practice follows current recommended practice to treat COPD in a stepwise manner

by maximising use of LAMA/LABA combination therapy and limiting use of long-term ICS due to similar efficacy but inferior safety for ICS over LABA.

6.32 The PBAC was concerned that the trade names and proliferation of inhalers for COPD may be points of confusion for prescribers and patients. The PBAC considered that quality use of medicines issue exists where this potential confusion may lead to use of multiple LABAs and associated clinical consequences.

6.33 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. Further, the PBAC considered that in the case of ICS/LABA products for COPD, the clinical place is evolving due to emerging evidence regarding the safety of ICS in this condition. The PBAC contrasted this with the treatment of asthma, and considered that ICS/LABA FDC products for asthma have a long established clinical place.

6.34 In the absence of the single components being available, patients with COPD cannot be treated in the stepwise manner recommended without changing the ICS and LABA medications. The PBAC noted the advice of the TSANZ that the low utilisation of single-agent salmeterol and eformoterol, which are not PBS-listed for COPD, suggests that prescribers are commencing treatment of COPD with ICS/LABA FDCs. TSANZ considered that the widespread use of ICS would expose patients with COPD to side effects, particularly pneumonia.

6.35 In view of the evolving clinical place of ICS/LABA combinations in COPD and the safety concerns regarding the use of ICS in COPD, the PBAC considered that its concerns regarding the availability of the FDC in the absence of the components were not addressed.

7 PBAC Outcome

7.1 The PBAC rejected the submission requesting PBS-listing for FF/VI 100/25 for the treatment of COPD. The PBAC did not accept the submission's claim that FF/VI 100/25 is non-inferior in terms of safety compared to FP/SAL 500/50. Further, the PBAC considered that there was no clear unmet clinical need for FF/VI in COPD particularly in light of the changing clinical place of ICS in COPD.

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

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

7.4 The PBAC considered that the submission's claim with regard to comparative safety was not supported. The PBAC considered that the cardiovascular risk associated with FF/VI was a significant comparative safety concern. Overall, the PBAC considered that the short duration of the trial precluded the possibility of concluding that FF/VI 100/25 and FP/SAL 500/50 are non-inferior in terms of comparative safety.

7.5 The PBAC raised a number of safety concerns regarding the FF/Vl FDC: the different dosing in patients with asthma and COPD may be problematic in patients with both asthma and COPD; that neither component of the FDC is available as a single

product; there is limited long term safety data for vilanterol; cardiovascular concerns have been raised in regard to very long acting LABAs in patients with COPD; and concerns have been raised about the risk of pneumonia in regard to the use of ICS in COPD. The PBAC considered this in the context of the evolving clinical place of ICS/LABA FDCs in the management of COPD.

7.6 Further, 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 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.

7.7 The PBAC further noted that there are two other ICS/LABA FDCs currently listed on the PBS for COPD. The PBAC considered that the clinical need for a third ICS/LABA was unclear, particularly in light of the comparative safety concerns associated FF/VI, and also the safety of the use of ICS therapy in COPD more generally.

7.8 The PBAC noted and welcomed the input received from the TSANZ in relation to the clinical place of ICS/LABA products in the treatment of COPD.

7.9 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 Breo available for Australian COPD patients.

The Sponsor strongly disagrees with the PBAC that the cardiovascular (CV) risk associated with fluticasone furoate/vilanterol (FF/VI) 100/25 in patients with COPD presents a significant comparative safety concern. The PBAC's finding is based on one 12 week trial, despite the evidence across the complete FF/VI programme, that no CV risk was identified. Indeed the 6 month placebo controlled studies (HZC102206/HZC102207, FF/VI 100/25: N =410) demonstrated that FF/VI 100/25 is associated with a low rate of CV events similar to patients receiving placebo. GSK are disappointed that despite the evidence to the contrary the PBAC continue to focus on this un-supported CV risk.

GlaxoSmithKline note that the referenced Quebec health insurance database study (Item 6.17) did not include fluticasone furoate/vilanterol.