5.8 FLUTICASONE FUROATE AND VILANTEROL TRIFENATATE, fluticasone furoate 100 microgram/actuation + vilanterol trifenatate 25 microgram/actuation, inhalation: powder for, 30 actuations and fluticasone furoate 200 microgram/actuation + vilanterol trifenatate 25 microgram/actuation, inhalation: powder for, 30 actuations Breo® Ellipta® GlaxoSmithKline Australia Pty Ltd

1 Purpose of Application

1.1 The submission requested a Restricted Benefit General Schedule listing for fluticasone furoate and vilanterol in a fixed dose combination (FDC) in two strengths of 100micrograms /25 micrograms and 200micrograms/25micrograms for the treatment of asthma.

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
FLUTICASONE FUROATE/VILANTEROL TRIFENATATE			
Dried powder for inhalation			Breo Ellipta GSK
100mcg/25mcg (30 Actuations)	1	5	
200mcg/25mcg (30 Actuations)	1	5	

Restricted benefit

Breo Ellipta is indicated in the regular treatment of asthma in adults and adolescents aged 12 years and older, where use of a combination product (long acting beta-2 agonist and inhaled corticosteroid) is appropriate, in patients who are symptomatic with inhaled corticosteroids and 'as needed' inhaled short-acting beta-2 agonist or patients already on both an inhaled corticosteroid and a long acting beta-2 agonist

2.1 The product presented is a dry powder inhaler with fluticasone furoate present as the furoate salt and vilanterol as the trifenatate salt (FF/VI).

2.2 Listing was sought based on a cost minimisation analysis compared to fluticasone proprionate/salmeterol (FP/SAL) fixed dose combination (FDC) for inhalation.

2.3 The PBAC agreed with the Secretariat comments that the restriction for FF/VI FDC should be consistent with the restrictions for the other inhaled corticosteroid (ICS)-long-acting beta agonist (LABA) FDCs listed for asthma maintenance therapy. The PBAC considered that the restriction wording should restrict the use of FF/VI FDC to patients who are 12 years or older. This is consistent with the TGA approved product information and with the clinical trials presented in the submission.

3 Background

3.1 The submission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration, a positive Delegate's Summary and a positive ACPM outcome were available.

3.2 The submission has not been considered by PBAC previously.

4 Clinical place for the proposed therapy

4.1 Asthma is a chronic inflammatory condition characterised by wheeze, chest tightness, cough and shortness of breath as a consequence of bronchoconstriction, airway inflammation and increased airway responsiveness (GINA, 2013). According to the National Asthma Council (NAC) 2014 guidelines, treatment with a preventer medication (usually ICS) is indicated for patients with regular symptoms of asthma. Patients with poor control of asthma while on ICS therapy may require the addition of a LABA to improve symptoms.

4.2 The submission proposed FF/VI FDC will substitute for existing ICS/LABA combinations.

5 Comparator

5.1 The submission nominated fluticasone proprionate/salmeterol (FP/SAL) fixed dose combination (FDC) as the comparator.

5.2 The PBAC considered that the nominated comparator is appropriate. The PBAC also agreed with the ESC that budesonide/eformoterol (BUD/FOR) FDC would also be another comparator.

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 there were no consumer comments on FF/VI FDC for the treatment of asthma.

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 250/50 twice daily (Trial HZA113091) and an indirect comparison between FF/VI 200/25 once daily (one trial; Trial HZA106829) and FP/SAL 500/50 twice daily (two trials; Trials SFCB3019 and SFCB3023), using fluticasone proprionate 500mcg twice daily as the common comparator. Key features of trials are shown in the table below.

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Direct evidence: FF/VI 100/25 OD vs FP/SAL 250/50 BID					
HZA113091	806	R, DB 24 weeks	Low	Asthma treated with medium dose ICS (FP 250 or equivalent)	Weighted mean serial FEV1, change in baseline trough FEV1 at day 168
Indirect evidence: FF/VI 200/25 OD vs FP/SAL 500/50 BD (Common comparator FP500 BID)					
FF/VI 200/25 OD vs FP 500 BD					

HZA106829	392[a]	R, DB 24 weeks	Low	Asthma treated with high dose ICS (FP 500 or equivalent)	Mean change from baseline in clinic visit trough FEV1 at 24 weeks
FP/SAL 500/50 BD vs FP 500 BD					
SFCB3019	503[b]	R, DB 28 weeks	Low	Reversible airways obstruction treated with fluticasone proprionate 750-1000mcg daily or equivalent	Mean change from baseline in clinic visit trough FEV1 at week 28
SFCB3023	509[c]	R, DB 12 weeks	Low		Mean change from baseline in clinic visit trough FEV1 at week 12
Meta-analysis	1012	Includes SFCB3019 and SFCB3023, assessed change in trough FEV1			Mean change from baseline in clinic visit trough FEV1 at end of study

DB=double blind, R = randomised, FF/VI = fluticasone furoate/vilanterol, FP/SAL = fluticasone proprionate/salmeterol, FP = fluticasone proprionate, OD = once daily, BD = twice daily

[a] includes only patients randomised to FF/VI or FP

[b] includes two different FP/SAL arms: one given fixed dose combination and one given both drugs concurrently

[c] includes two different FP/SAL arms: FP/SAL 500/50 1 actuation BD and FP/SAL 250/25 2 actuations BD

Source: Table 1 p3 of the commentary

6.4 The PBAC noted that there were differences in the baseline FEV1 in patients enrolled in Trial HZA106829 and those enrolled in Trials SFCB3019 and SFCB3023 which may bias the results of the indirect comparison (FF/VI 200/25 OD vs. FP/SAL 500/50 BD) including:

- patients enrolled in Trial HZA106829 had a lower baseline FEV1 and percent predicted FEV1 compared to patients enrolled in Trials SFCB3019 and SFCB3023, indicating that there was more potential for improvement in patients enrolled in Trial HZA106829;
- patients randomised to FF/VI in Trial HZA106829 had generally lower baseline FEV1 than FP/SAL patients in Trials SFCB3019 and SFCB3012. For example, the average baseline FEV1 which was 0.161L lower than patients randomised to FP/SAL MDI in Trial SFCB3019. The 0.161L difference was greater than the MCID (0.15L) proposed in the submission; and
- there was a difference, albeit small in magnitude (around 0.10L) in the baseline lung function between the fluticasone propionate 500mcg groups in Trial HZA106829 compared to Trials SFCB3019 and SFCB3023 and may indicate that patients randomised to the 'common comparator' in the trials were not comparable and may confound the results of the indirect comparison.

6.5 A summary description of the trials presented in the submission is shown in the table below.

Trial	**Protocol title/ Publication title**	**Publication citation**
Direct randomised trials		
FF/VI 100/25 OD versus FP/SAL 250/50 BID		
HZA113091	A Randomised, Double-Blind, Double-Dummy, Parallel Group, Multicentre Study to assess efficacy and safety of Fluticasone Furoate (FF)/GW642444 Inhalation Powder and Fluticasone Propionate (FP)/Salmeterol Inhalation Powder in the treatment	30 April 2012 Chest. 2013;144(4):1222-1229

	of Persistent Asthma in Adults and Adolescents	
FF/VI 200/25 OD versus FP 500 BID		
HZA106829	A Randomised, Double-Blind, Parallel Group, Multicentre Study of Fluticasone Furoate/GW642444 Inhalation Powder, Fluticasone Furoate Inhalation Powder Alone, and Fluticasone Propionate Alone in the Treatment of Persistent Asthma in Adults and Adolescents.	30 April 2012
FP/SAL 500/50 BD versus FP 500 BID		
SFCB3019	Salmeterol/fluticasone propionate (50/500 mcg) in combination in a DISKUS inhaler (Seretide) is effective and safe in the treatment of steroid-dependent asthma.	Full CSR: 1 April 1998 Respiratory medicine. Dec 1999; 93(12):876-884
SFCB3023	Clinical Equivalence of a Salmeterol/Fluticasone Propionate Combination Product (50/500mcg) Delivered via a Chlorofluorocarbon-Free Metered-Dose Inhaler with the DISKUS in Patients with Moderate to Severe Asthma.	Full CSR: 24 August 2000 Clinical drug investigation. 2001; 21(4):243-255

Comparative effectiveness

6.6 Results of direct and indirect comparisons were show in the table below.

Trial	**Fluticasone furoate + vilanterol**	**Fluticasone propionate + salmeterol**	**Fluticasone**	**Mean difference (95% CI)**
FF/VI 100/25 vs FP/SAL 250/50 – direct comparison Primary outcome: Change from baseline in weighted mean for 24 h serial FEV1 in Litres at Day 168 (LS mean change from pre-dose (SE)); non-inferiority criteria: 0.15L				
HZA113091	n/N = 352/403 0.341 (0.0184)	n/N =347/403 0.377 (0.0185)	NA	-0.037 (-0.088, 0.015)
FF/VI 100/25 vs FP/SAL 250/50 – direct comparison Secondary outcome: Change from baseline in pre-dose (Trough FEV1 in litres) at day 168 (LS mean change from baseline(SE)); non-inferiority criteria: 0.15L				
HZA113091	n/N = 397/403 0.281 (0.0191)	n/N =389/403 0.3 (0.0193)	NA	-0.019 (-0.0723, 0.034)
FF/VI 200/25 vs FP/SAL 500/50 – indirect comparison Primary outcome: Mean change from baseline in trough FEV1 (LS mean change from baseline (SD)); non-inferiority criteria:0.15L				
HZA106829	n/N = 187/197 0.394 (0.413)	NA	n/N = 190/195 0.183 (0.4135)	0.210 (0.127, 0.294)
HZA106829 – excl 040688	[redacted]	[redacted]	[redacted]	[redacted]
SFCB3019	NA	n/N = 283/338 0.204 (0.4759)	n/N = 128/165 0.210 (0.4525)	-0.006 (-0.1020), 0.0900)
SFCB3023	NA	n/N = 295/337 0.246 (0.3646)	n/N = 147/172 0.130 (0.3637)	0.116 (0.044, 0.188)
Meta-analysis (SFCB3019&3023)	[redacted]	[redacted]	[redacted]	[redacted]
Indirect comparisons				
HZA106829 vs SFCB3019				[redacted]
HZA106829 vs SFCB3023				[redacted]
HZA106829 vs Meta-analysis (SFCB3019&3023)				[redacted]
HZA106829 – excl 040688 vs Meta-analysis (SFCB3019&3023)				[redacted]

	[redacted]

Abbreviations: FF/VI = Fluticasone Furoate/Vilanterol, FP/SAL = Fluticasone Proprionate/Salmeterol NA = Not Applicable, SD = Standard deviation SE = Standard Error; LS=least squares. Note: numbers behind FF/VI and FP/SAL refer to the strength of the relevant component of the fixed dose combination in micrograms. Text in italics indicates values calculated during evaluation using excel.
Source: Table 25, p69, Table 26, p70, Table 71, pp138-139 of the submission, Spreadsheet 'FFVI_SPSAL_IndirectAnalysis_pub.xlsx

6.7 The PBAC noted that:

- Trial SFCB3019 included treatment arms in which fluticasone propionate and salmeterol were used as the combination product (Seretide®) or concomitantly. The results combining the two treatment regimens were presented.
- Trial SFCB3023 included treatment arms in which the FP/SAL FDC was administered via a MDI or DPI, which were assumed to be equivalent and the efficacy results had been combined.
  A sensitivity analysis around results of Trial HZA106829 was presented which excluded data for 48 subjects associated with Investigator 040688. This was due to "…issues with Good Clinical Practice identified during a site audit".

6.8 The PBAC considered that results from direct comparison are reasonably reliable and applicable to the likely PBS population.

6.9 The PBAC noted the ESC's concerns about concluding non-inferiority given the exchangeability issues in the indirect comparison of the higher dose forms but considered that it was reasonable on the basis of all the evidence presented to conclude that non-inferiority was established at the higher strengths.

Comparative harms

6.10 Amongst all clinical studies with FF and/or VI (including trial HZA113091), a total of 2,652 patients with asthma received at least one dose of FF/VI. Regarding the safety of FF/VI compared with FP/SAL, the PBAC noted that an overall rate of pneumonia of 8.4 patients with an event per 1000 treatment years in FF/VI 100/25 and 18.4 patients with an event/1000 treatment years in FF/VI 200/25. The PBAC considered that the risk of pneumonia with FF/VI would not be expected to be different from other marketed ICS/LABA products. Rates of key adverse events such as pneumonia, local steroid events or change in urine cortisol appeared to be similar in patients treated with FF/VI and FP/SAL.

6.11 The PBAC noted that there was a difference in cardiovascular events reported. The PBAC considered that long acting LABAs, such as vilanterol should be monitored as emerging evidence showed that they may increase cardiac event risks.

Clinical claim

6.12 The submission claimed the FF/VI FDC as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over the FP/SAL FDC. The PBAC considered this claim was reasonable.

Economic analysis

6.13 Economic analysis was based on a cost minimisation comparing FF/VI FDC with FP/SAL FDC.

6.14 The equi-effective doses were estimated as:

- FF/VI 100/25mcg once daily was equivalent to FP/SAL 250/50mcg (DPI) twice daily based on direct trial evidence (Trial HZA113091); and
- FF/VI 200/25mg once daily was equivalent to FP/SAL 500/50mcg (DPI) twice daily based on indirect evidence (Trial HZA106829 versus Trials SFCB3019 and SFCB3023).The PBAC agreed with the ESC that there was less confidence in the equi-effective dose from the indirect analysis.

Estimated PBS usage & financial implications

6.15 The submission used a market-based approach assuming substitution of fluticasone propionate /salmeterol (FP/SAL) and budesonide/eformoterol (BUD/FOR). The PBAC noted that the submission assumed no market growth but considered that some market growth is possible. The convenience of a once daily formulation may promote greater use and increase substitution of single agent ICS preparations by fixed dose combinations of ICS/LABA.

6.16 The submission's proposed savings in the net cost are based on the assumption of substitution for BUD/FOR 400/12.

6.17 Estimated use and financial implications are shown in the table below.

	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 extent of use FF/VI 200/25					
Utilisation number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS/RPBS/MBS (Asthma only)					
Net cost to PBS	[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]

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

6.18 The likely number of packs dispensed per year was estimated in the submission to be over 200,000 in Year 5, at an estimated net saving per year to the PBS of less than $10 million in Year 5.

6.19 The PBAC noted the QUM concerns raised by ESC including:

- The potential for higher use in children owing to the perceived advantage of once daily dosing in some children. The PBAC has previously noted the higher than expected use of FDCs in children younger than 12 years, including some use of dry powder inhalers in younger children;
- There is no lower strength of FF/VI comparable to FP/SAL 100/50 although the PBAC noted that current utilisation of this low strength is predominantly in children less than 12 years of age. The lack of a very low strength reduces the ability to down titrate the strength of ICS; and
- There are no PBS listed single components and titration to the FDC will be from the alternative fluticasone product, used twice daily, or another ICS.

Although the PBAC recommended restriction limits use of this product to children over 12 years of age, PBAC considered the concerns about use in this population remain relevant because of the potential for use outside of the restriction.

6.20 The PBAC noted the sponsor's pre-PBAC offer of [redacted]% price reduction to the Dispensed Price Maximum Quantity initially proposed by the submission.

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. However, the PBAC considered that in the case of LABA/ICS FDC products for asthma, these products have a long established clinical place. The PBAC also noted that current best clinical practice in asthma treatment no longer requires stabilisation the individual components prior to using a LABA/ICS FDC. The PBAC contrasted this with the treatment of chronic obstructive pulmonary disease (COPD), and considered that the place of LABA/ICS FDC products for COPD is still evolving.

6.22 The PBAC noted the advice of the sponsor, tabled at the meeting, that the Product Information (PI) will include a table directing prescribers on how to switch patients from existing products onto FF/VI FDC.

6.23 In view of significant clinical experience with LABA/ICS FDCs in asthma and the availability of advice on switching from existing products, the PBAC considered that its concerns regarding the availability of the FDC in the absence of the components were addressed. The PBAC nonetheless considered that it would be prudent to closely monitoring the listing, and requested that the National Prescribing Service address this issue in a future publication.

7 PBAC Outcome

7.1 The PBAC recommended PBS listing of fluticasone furoate with vilanterol (dry powder inhaler) on a cost minimisation basis to fluticasone propionate with salmeterol (dry powder inhaler and metered dose inhaler). The equi-effective doses are FF/VI 100microgram/25microgram once daily to FP/SAL 250microgram/50 microgram (dry powder inhaler) twice daily and FF/VI 200microgram/25microgram once daily to FP/SAL 500microgram/50 microgram (dry powder inhaler) twice daily.

7.2 The PBAC agreed that the restriction for FF/VI FDC should be consistent with the restrictions for the other ICS-LABA FDCs listed for asthma maintenance therapy, but that the PBS-subsidised use of FF/VI FDC should be additionally restricted to patients who are 12 years or older. This is consistent with the TGA approved product information and with the clinical trials presented in the submission.

7.2 The PBAC accepted FP/SAL FDC is the main comparator. While evidence comparing FP/SAL with BUD/FOR was not presented in the submission the PBAC considered that, based on previous considerations of FP/SAL and BUD/FOR that it was reasonable to assume similar benefit.

7.3 The PBAC noted that financial estimate presented in the submission included substitution for BUD/FOR 400/12, which has a higher DPMQ than FF/VI and resulted in cost savings. However, the PBAC considered that the extent of substitution for BUD/FOR 400/12 was poorly substantiated. Assuming no substitution from BUD/FOR results in a net cost to the PBS at the price initially proposed by the submission. [redacted]

7.4 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, and there is limited long term safety data for vilanterol and cardiovascular concerns have been raised in regard to very long acting LABAs. The PBAC weighed this against the significant clinical experience with ICS/LABA FDC products in asthma, and the advice that the PI will include direction for prescribers on how to switch patients from currently-listed products. The PBAC therefore considered that it was reasonable to recommend the listing of the FDC in the absence of the components. The PBAC requested that the NPS address these issues in a future publication.

7.5 The PBAC recommended FF/VI FDC like other ICS-LABA FDC be included in the PBS medicines for prescribing by nurse practitioners within collaborative arrangements.

7.6 Advice to the Minister under Subsection 101 3BA of the National Health Act
In accordance with subsection 101(3BA) of the National Health Act 1953, the PBAC advised that it is of the opinion that, on the basis of the material available to it at its March 2014 meeting the combination drug fluticasone furoate with vilanterol should be treated as interchangeable on an individual patient basis with the combination drugs fluticasone propionate with salmeterol; budesonide with eformoterol; and fluticasone propionate with eformoterol; when these drugs are used to treat asthma.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
FLUTICASONE FUROATE/VILANTEROL TRIFENATATE				
Dried powder for inhalation			Breo Ellipta	GSK
100mcg/25mcg (30 Actuations)	1	5		
200mcg/25mcg (30 Actuations)	1	5		

Condition:	Asthma
Restriction:	Restricted benefit
Clinical criteria:	Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids.
Population criteria:	Patient must be aged 12 years or over.
Administrative Advice	***Note*** *This drug is not recommended nor PBS-subsidised for use as 'maintenance and reliever' therapy.* ***Note*** *This drug is not PBS-subsidised for the treatment of Chronic Obstructive Pulmonary Disease (COPD).*

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 welcomes the PBAC's recommendation to list Breo for the treatment of asthma on the PBS.

In regards to paragraph 6.11 GSK wishes to clarify that this point refers to Breo use in COPD not asthma. For further information please refer to the sponsor comments section on the Breo 100/25 for use in COPD Public Summary Document March 2014.