

7.10 FLUTICASONE+VILANTEROL, dry powder inhaler, fluticasone furoate 100 microgram/actuation + vilanterol (as trifenatate) 25 microgram/actuation, Breo[®] Ellipta[®], GlaxoSmithKline Australia Pty Ltd.

1 Purpose of Application

- 1.1 To request a Restricted Benefit listing for the symptomatic treatment of chronic obstructive pulmonary disease (COPD), in patients where FEV₁ is less than 50% of predicted normal, and where there is a history of repeated exacerbations with significant symptoms despite regular beta-₂ agonist bronchodilator therapy.

2 Requested listing

- 2.1 The submission requested the following restriction:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
FLUTICASONE AND VILANTEROL fluticasone furoate 100 microgram + vilanterol (as trifenatate) 25 microgram inhalation: powder for, 30 actuations	1	5	Breo [®] Ellipta [®] GSK

- 2.2 Listing was sought on a cost-minimisation basis with fluticasone/vilanterol (FF/VI) 100/25 compared to fluticasone/salmeterol (FP/SAL) 500/50 in the treatment of COPD.

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

3 Background

- 3.1 Fluticasone/vilanterol was TGA registered on 17 April 2014 for symptomatic treatment of patients with COPD with a FEV₁ <70% predicted normal (post-bronchodilator) in patients with an exacerbation history despite regular bronchodilator therapy. Fluticasone/vilanterol is not indicated for the initiation of bronchodilator therapy in COPD.
- 3.2 A major submission for fluticasone/vilanterol (FF/VI) 100/25 for the treatment of COPD was considered and rejected by the PBAC at its March 2014 meeting. The PBAC did not accept the submission's claim that FF/VI 100/25 is non-inferior in terms of safety compared to fluticasone propionate and salmeterol (FP/SAL) 500/50. Furthermore, 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 inhaled corticosteroids (ICS) in COPD.

4 Clinical place for the proposed therapy

- 4.1 This has not been changed from the March 2014 submission.

5 Comparator

- 5.1 The main comparator is FP/SAL 500/50. This was considered appropriate by the PBAC in March 2014.

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 No new trial data was presented.

Comparative effectiveness

- 6.4 In March 2014, the PBAC had been 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. The minor resubmission did not address this.

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

Comparative harms

- 6.5 The PBAC had considered the March 2014 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 (PBAC minutes, March 2014, paragraph 6.21). 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. The minor resubmission did not address the issue of the duration of the trial.

- 6.6 With regard to the PBAC's concern about the increased rate of cardiovascular events in the pivotal trial, the current submission claimed:

- That this is due to a statistical anomaly plausibly explained by the low number of patients reporting cardiovascular events on the FP/SAL 500/50 arm
- This is supported by placebo controlled studies (HZC112206 and HZC112207) that show risk of cardiovascular events to be similar to placebo
- This is supported by analyses across the three FF/VI 100/25 vs. FP/SAL studies, showing the risk of cardiovascular events to be similar across all treatments. Viewed within the context of the two other FP/SAL studies (HZC113109 and HZC112352) it can be concluded that the number of events on FF/VI in HZC113107 was not

unusually high but rather the number of events on FP/SAL 500/50 was unusually low, with only 1 event recorded in 262 COPD patients over 12 weeks.

- That an agreed risk minimisation plan with the TGA will monitor cardiovascular safety through standard post-marketing surveillance mechanisms and was not deemed to require a specific safety program outside of ICS/LABA class related monitoring.

6.7 With regard to the PBAC's concern about the risk of pneumonia in regard to the use of ICS in COPD, the submission claimed:

- That ICS/LABA associated pneumonia risk should be considered within the context of potential benefit and that ICS/LABA should be reserved for the treatment of high risk COPD patients in which the risk/benefit profile of increased pneumonia is off-set by a reduction in exacerbations and mortality.
- That FF/VI 100/25 does not pose an incremental pneumonia risk vs. FP/SAL 500/50.
- That the results of the direct comparison of pneumonia events on FF/VI 100/25 and FP/SAL 500/50 show that the incidence of pneumonia was comparable and that overall the exposure adjusted rate of pneumonia was similar across FF/VI 100/25 and FP/SAL 500/50 ([REDACTED]).

6.8 In March 2014, the PBAC also raised the following safety concerns regarding the FF/VI 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
- These concerns are not addressed in current submission.

Clinical claim

6.9 The March 2014 submission claimed that FF/VI 100/25 FDC is non-inferior in terms of comparative effectiveness over the FP/SAL 500/50 FDC in the treatment of COPD. The PBAC considered that the submission's claim with regard to comparative effectiveness was reasonable.

6.10 The current submission claimed non-inferior comparative effectiveness and non-inferior comparative safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol.

6.11 The PBAC considered that the claim non-inferior comparative effectiveness was reasonable.

6.12 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

6.13 The PBAC recalled that in March 2014, aclidinium (a LAMA), was recommended for listing on the PBS at the lower price requested by the sponsor. The PBAC noted that the Department's advice at the meeting that the Minister (through his Delegate) intends to declare aclidinium as a pharmaceutical benefit under section 85(2) of the *National Health Act 1953* and that the PBS listing will proceed with the lower price. As the main comparator in this submission, FP/SAL 500/50 is cost-minimised to aclidinium (via tiotropium), the PBAC considered it is appropriate for the new lower aclidinium price to be used in calculating the price for FF/VI.

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

Economic analysis

6.14 The minor submission did not present a new economic analysis.

Estimated PBS usage & financial implications

6.15 The PBAC noted that as FF/VI was dosing once daily compared with twice daily for FP/SAL, patient preference for a once daily dose may drive utilisation. The PBAC considered however that once daily compared with twice daily dosing was unlikely to yield an adherence benefit.

6.16 The PBAC noted that at the price recommended, the listing would be expected to result in a saving to Government.

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of fluticasone with vilanterol, in the form fluticasone furoate with vilanterol (as trifenatate), 100/25 as a restricted benefit for the treatment of COPD with a maximum quantity of one pack with five repeats.

7.2 The PBAC agreed that the main comparator is the existing ICS/LABA, FP/SAL 500/50 when used for the treatment of COPD.

7.3 The PBAC considered that the cost-effectiveness of fluticasone with vilanterol would be acceptable if it were cost-minimised against aclidinium, which was recommended for listing by PBAC in March 2014 for the same indication but at the lower price requested by the sponsor and which is, in turn, cost-minimised to the comparator via tiotropium. The PBAC noted that the Department's advice at the meeting that the Minister (through his Delegate) intends to declare aclidinium as a pharmaceutical benefit under section 85(2) of the *National Health Act 1953* and that the PBS listing will proceed with the lower price.

7.4 The equi-effective doses are FF/VI 100/25 once daily and FP/SAL 500/50 twice daily.

7.5 The PBAC considered that the data presented adequately supported the submission's claim that FF/VI is non-inferior in terms of comparative effectiveness and comparative safety when compared to fluticasone/salmeterol.

7.6 The PBAC noted that at the time of its previous decision, FF/VI 100/25, was not yet TGA registered for the treatment of COPD. The PBAC note the FF/VI 100/25 is now TGA registered for '*symptomatic treatment of patients with COPD with a FEV₁ <70% predicted normal (post-bronchodilator) in patients with an exacerbation history despite regular bronchodilator therapy. Fluticasone/vilanterol is not indicated for the initiation of bronchodilator therapy in COPD*'.

7.7 The PBAC recalled that in March 2014 they had concerns about the comparative safety of FF/VI in relation to cardiovascular events. The PBAC note that the increased risk of cardiovascular events was only seen in the HZC113107 trial, and has not been seen or replicated in any other study. The PBAC was further reassured in relation to the comparative safety of FF/VI by the fact that an agreed risk minimisation plan with the TGA will monitor cardiovascular safety through standard

post-marketing surveillance mechanisms and it was not deemed to require a specific safety program outside of ICS/LABA class related monitoring.

- 7.8 The PBAC acknowledged that increased risk of pneumonia with ICS preparations is not exclusive to FF/VI, but applies to all ICS/LABA preparations. The PBAC also noted that the TORCH trial showed that although the rates of pneumonia were increased in patients treated with ICS/LABA, this was offset by a 25% reduction in COPD related exacerbations.
- 7.9 The PBAC noted that the approved Product Information contains information for prescribers in relation to switching between other inhalers due to the unavailability of the individual components. The PBAC noted that the section of its Guidelines dealing with fixed dose combination products notes that it is preferable to have the individual components to available separately. The PBAC considered that the concern in relation to the individual components not being available was less given that this would not be the first ICS/LABA to be made available on the PBS.
- 7.10 The PBAC considered that in light of this recommendation, the fixed dose combination guidelines should be reviewed.
- 7.11 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 fluticasone furoate/vilanterol should be treated as interchangeable on an individual patient basis with fluticasone/salmeterol and budesonide/eformoterol for the treatment of COPD.
- 7.12 The PBAC advised that fluticasone furoate/vilanterol is suitable for prescribing by nurse practitioners.
- 7.13 The PBAC recommended that the Safety Net 20 Day Rule should not apply.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Manufacturer	Name and
FLUTICASONE FUROATE AND VILANTEROL fluticasone furoate 100 microgram + vilanterol (as trifenatate) 25 microgram inhalation: powder for, 30 actuations	1	5	Breo® Ellipta®	GSK

Condition/Indication:	Chronic obstructive pulmonary disease (COPD)
Restriction:	Restricted benefit

Clinical criteria:	<p>Patient must have a forced expiratory volume in 1 second (FEV₁) less than 50% of predicted normal prior to therapy,</p> <p>AND</p> <p>Patient must have a history of repeated exacerbations with significant symptoms despite regular beta-2 agonist bronchodilator therapy,</p> <p>AND</p> <p>The treatment must be for symptomatic treatment.</p>
Administrative Advice <i>(not included in LI)</i>	<p>Note: Patients must not be on a concomitant single agent long-acting beta-2 agonist.</p> <p>Note: This product is not indicated for the initiation of bronchodilator therapy in COPD.</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

GlaxoSmithKline welcomes the PBAC's recommendation to list Breo 100/25mcg for the treatment of COPD on the PBS.