

The PBAC made further recommendations regarding the naming of the drug fluticasone furoate and other related matters under Section 85(2) of the National Health Act 1953, at its March 2017 meeting (item 7.03 fluticasone furoate Public Summary Document refers).

**5.07 FLUTICASONE, powder for oral inhalation in breath actuated device containing fluticasone furoate 100mcg and 200mcg per dose, Arnuity® Ellipta®, GlaxoSmithKline.**

**1 Purpose of Application**

1.1 To request an unrestricted listing on the general schedule for fluticasone furoate (FF).

**2 Requested listing**

2.1 An unrestricted listing was requested, consistent with other inhaled corticosteroid (ICS) monotherapy currently listed on the PBS. Secretariat amendments are shown below in italics with deletions shown in strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
FLUTICASONE FUROATE, Dry powder inhaler 100mcg	1	5	\$ [REDACTED]	Arnuity® GlaxoSmithKline
Dry powder inhaler 200mcg	1	1	\$ [REDACTED]	Ellipta®

Episodicity	<del>Chronic</del>
Severity	Not applicable
Condition	<del>Asthma</del>
Restriction	Unrestricted
Treatment criteria	Not applicable
Clinical criteria	Not applicable
Population criteria	Not applicable

2.2 The basis for listing is a cost-minimisation against fluticasone in the form fluticasone propionate (FP).

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

**3 Background**

3.1 The submission was made under TGA/PBAC Parallel Process. At the time of evaluation, the Clinical Evaluation Report was available. FF was registered on the ARTG on 11 September 2015, without ACPM consideration and is indicated for the maintenance treatment of asthma in patients aged 12 years and over.

3.2 FF as monotherapy has not been considered by the PBAC previously.

#### **4 Clinical place for the proposed therapy**

4.1 Asthma is a chronic disease of the lungs characterised by airway inflammation, bronchoconstriction and increased airway responsiveness. Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g. eosinophils, macrophages, lymphocytes) and mediators (e.g. cytokines and chemokines) involved in inflammation, and inhaled corticosteroids (ICS) are considered the most effective preventer medicine in asthma.

4.2 FF 100mcg is expected to have the same clinical place of therapy as other mid-dose ICS monotherapies whilst FF 200mcg is expected to have the same clinical place as other high-dose ICS monotherapies.

4.3 The ESC noted that as the ICS/LABA combination FF/VI (fluticasone furoate with vilanterol) is currently listed, it is reasonable to have the individual ICS component listed.

#### **5 Comparator**

5.1 Fluticasone propionate (FP) was nominated as the comparator. The evaluation noted that this is not the only appropriate comparator. Whilst FP is the only other ICS that is available in a high-dose (FP 500mcg) preparation, other ICS which have a mid-dose equivalence, such as beclomethasone, ciclesonide and budesonide should also be considered as comparators for FF 100mcg. The Pre-Sub-Committee Response (p3) maintained that FP is the most appropriate comparator.

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

#### **6 PBAC consideration of the evidence**

##### ***Sponsor hearing***

6.1 There was no hearing for this item.

##### ***Consumer comments***

6.2 The PBAC noted that no consumer comments were received for this item.

##### ***Clinical trials***

6.3 The submission is based on four head-to-head trials:

- two comparing FF 100mcg once daily to FP 250mcg twice daily (number randomised to receive either treatment=433); and
- two comparing FF 200mcg once daily to FP 500mcg twice daily (number randomised to receive either treatment=598).

Note that all four trials also randomised patients to receive other therapies (including placebo and other doses of FF).

6.4 Details of the trials presented in the submission are provided in Table 1.

**Table 1: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Direct randomised trials</b>		
FFA112059	A randomised, double-blind, double-dummy, placebo controlled (with rescue medication), multicenter study to evaluate the efficacy and safety of fluticasone furoate inhalation powder in the treatment of persistent asthma in adults and adolescents  Lotvall J, Bleecker ER, Busse WW, O'Byrne PM, Woodcock A, Kerwin EM, Stone S, Forth R, Jacques L, Bateman ED: Efficacy and safety of fluticasone furoate 100µg once-daily in patients with persistent asthma: a 24-week placebo and active-controlled randomised trial.	Clinical Study Report, effective 13 April 2012  Respir Med 2014; 108(1):41-9.
FFA109685	A randomised, double-blind, double-dummy, placebo-controlled, parallel-group, multicenter dose ranging study to evaluate the efficacy and safety of GW685698X inhalation powder once daily and fluticasone propionate inhalation powder 250 mcg twice daily compared with placebo for 8 weeks in adolescent and adult subjects with persistent asthma symptomatic on low-dose ICS therapy  Bleecker ER, Bateman ED, Busse WW, Woodcock A, Frith L, House KW, Jacques L, Davis AM, Haumann B, Lotvall J: Once-daily fluticasone furoate is efficacious in patients with symptomatic asthma on low-dose inhaled corticosteroids	Clinical Study Report, effective 15 May 2012  Ann Allergy Asthma Immunol. 2012; 109 (5): 353-358.
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  O'Byrne PM, Bleecker ER, Bateman ED, Busse WW, Woodcock A, Forth R, Toler WT, Jacques L, Lotvall J: Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma.	Clinical Study Report, effective 30 April 2012  Eur Respir J 2014; 43(3): 773-82.
FFA109684	A randomised, double-blind, double dummy, placebo-controlled, parallel-group, multicenter dose ranging study to evaluate the efficacy and safety of GW685698X inhalation powder once daily and fluticasone propionate inhalation powder 500 mcg twice daily compared with placebo for 8 weeks in adolescent and adult subjects with persistent asthma symptomatic on moderate-dose ICS therapy  Busse WW, Bleecker ER, Bateman ED, Lotvall J, Forth R, Davis AM, Jacques L, Haumann B, Woodcock A: Fluticasone furoate demonstrates efficacy in subjects with asthma symptomatic on medium doses of inhaled corticosteroid therapy: An 8-week, randomised, placebo-controlled trial.	Clinical Study Report, effective 15 May 2012  Thorax 2012; 67: 35-41.
Bateman 2012	Bateman ED, Bleecker ER, Lotvall J, Woodcock A, Forth R, Medley H, Davis AM, Jacques L, Haumann B, Busse WW. Dose effect of once-daily fluticasone furoate in persistent asthma: A randomized trial.	Resp Med 2012; 106: 642-50

Source: Table 6, pp35-36 of the submission

6.5 Bateman (2012) was identified by the submission during the literature search but was excluded on the basis that the trial did not include the proposed treatment and the main comparator in separate treatment arms. The evaluation noted this is inaccurate as the trial reported by Bateman (2012) treated patients with FF 100mcg and 200mcg once daily as well as FP 100mcg twice daily in different arms of the study. Exclusion on the basis of doses compared may be problematic as this indicates that dose equivalence between FF and FP was pre-selected and may not be based on all

available evidence. A brief description and results of the Bateman (2012) trial are summarised below.

6.6 The key features of the direct randomised trials are summarised in Table 2.

**Table 2: Key features of the included evidence**

Trial	N <sup>1</sup>	Design/ duration	Risk of bias	Patient population	Outcomes
<b>FF 100 vs FP 250</b>					
FFA112059	228	DB,MC,R / 24 weeks	Low	Asthma, age ≥12 years	Mean change from baseline in trough FEV1
FFA109685	205	DB,MC,R / 8 weeks	Low		
<b>FF 200 vs FP 500</b>					
HZA106829	389	DB, MC, R / 24 weeks	Low	Asthma, age ≥12 years	Mean change from baseline in trough FEV1
					Change from baseline in weighted mean serial FEV1 over 24 hours
FFA109684	209	DB, MC, R / 8 weeks	Low		Mean change from baseline in trough FEV1

<sup>1</sup> N refers to only patients who were treated with the dosage relevant to the comparison. All trials included treatment arms beyond the FF and FP doses listed here.

DB=double blind; MC=multi-centre; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised.  
Source: compiled during the evaluation

6.7 It should be noted that Trials FFA112059, FFA109685 and FFA 109684 were not powered to detect non-inferiority between FF and FP, and that results from these three trials are likely to be biased towards a non-significant result. Only trial HZA106829 was powered to detect non-inferiority between FF and FP, and non-inferiority would be demonstrated if the lower limit of the confidence interval (CI: 0.025, 1-sided significance level) for the mean difference in change from baseline in clinic visit trough FEV1 of FF 200mcg OD versus FP 500mcg BD was greater than -125mL. This margin is likely to be reasonable as it is narrower than those previously accepted by the PBAC of -200mL (Fluticasone propionate/eformoterol PSD July 2013, p4) and -150mL (Fluticasone furoate/vilanterol PSD March 2014, p4). The PSCR (p2) acknowledged that the trials were not originally powered to establish non-inferiority but maintained that the meta-analysis is sufficiently powered to conclude non-inferiority.

6.8 Bateman (2012) was a randomised, double-blind, double-dummy, parallel-group, placebo- and active-controlled trial which enrolled 601 patients aged ≥12 years with persistent asthma not optimally controlled on SABA or other non-steroidal controllers. Patients were randomised to FF 25mcg, 50mcg, 100mcg or 200mcg once daily, FP 100mcg twice daily or placebo; and treated for 8 weeks.

### **Comparative effectiveness**

6.9 Tables 3 and 4 summarise the mean change from baseline in trough FEV1 levels in the trials identified by the submission.

**Table 3: Results of mean change from baseline in trough FEV1: FF 100 vs FP 250**

Trial ID	FF 100, mean (SD), n	FP 250, mean (SD), n	LS mean difference (95% CI)
FFA112059 (24 weeks)	0.161 (0.0398), n=111	0.159 (0.0406), n=107	0.0020 (-0.1095, 0.1135)
FFA109685 (8 weeks)	0.142 (0.0403), n=102	0.160 (0.0409), n=99	( )
Pooled result from random effects model			( )

Source: Table 20 and 21, p83 of the submission

**Table 4: Results of mean change from baseline in trough FEV1: FF 200 vs FP 500**

Trial ID	FF 200, mean (SD), n	FP 500, mean (SD), n	LS mean difference (95% CI)
HZA106829 (24 weeks)	0.201 (0.0303), n=186	0.183 (0.0300), n=190	0.018 (-0.066, 0.102)
FFA109684 (8 weeks)	0.232 (0.0347), n=98	0.155 (0.0332), n=107	( )
Pooled result from random effects model			( )

Source: Table 20 and 21, p83 of the submission

- 6.10 Trial HZA106829 also reported change from baseline in weighted mean serial FEV1 over 24 hours as a co-primary outcome. The LS mean difference between FF 200mcg once daily and FP 500mcg twice daily was not statistically significantly different (0.070L (95%CI -0.065, 0.205)). The significance of change from baseline in weighted mean serial FEV1 over 24 hours is unknown as there is no non-inferiority margin nominated or identified.
- 6.11 There are two trials which randomised patients to FF 100mcg and FF 200mcg once daily (among other doses), Trial FFA109685 and a trial that was excluded by the submission on the basis that it did not provide a comparison of FF and FP at the specified doses (Bateman 2012). The results for the primary outcome from Trial FFA109685 and Bateman (2012), for the comparison of FF 100mcg and FF 200mcg once daily are summarised in Table 5.

**Table 5: LS mean change from baseline in pre-dose (trough) FEV1 at 8 weeks in trial FFA109685 and Bateman 2012**

Trial	FF 100mcg, LS mean (95% CI)	FF 200mcg, LS mean (95% CI)
FFA109685	0.207 (0.096, 0.318), n=102	0.238 (0.127, 0.349), n=101
Bateman 2012	0.341 (NR), n=109	0.367 (NR), n=94

Source: Table 11, FFA 109685 CSR and Bateman 2012

NR = not reported

- 6.12 Whilst neither trial was designed to test the relative efficacy of FF 100mcg and FF 200mcg, the evaluation noted that there does NOT appear to be a significant difference between FF 100mcg and FF 200mcg. This is further supported by the linear trend tests in the dose ranging studies (FFA109684, FFA109685 and Bateman 2012), which showed that there is a dose effect relationship for treatment with FF but not for doses beyond 100mcg. This implies that there may not be any clinical benefit of using FF 200mcg over FF 100mcg. Therefore, the necessity of having both FF 100mcg and 200mcg may need to be considered. The PSCR (p4) argued that each individual patient has their own dose response curve dependent upon severity of disease, and that higher doses of ICS continue to result in gains in PEF or FEV<sub>1</sub>. The ESC considered that some patients may derive a benefit from a higher dose of ICS, and that therefore having multiple strengths available would be clinically appropriate.

### Comparative harms

- 6.13 Table 6 summarises the incidence of on treatment adverse events in the four trials identified by the submission.

**Table 6: Summary of key adverse events in the direct randomised trials reported as n (%)**

Type of Adverse Event	FFA112059		FFA109685		HZA106829		FFA109684	
	FF 100 (n=114)	FP250 (n=114)	FF 100 (n=105)	FP 250 (n=100)	FF 200 (n=194)	FP 500 (n=195)	FF 200 (n=99)	FP 500 (n=110)
Local steroid effect	10 (9)	7 (6)	NR	NR	■ (■)	■ (■)	NR	NR
Bronchitis	8 (7)	4 (4)	-	-	6 (3)	6 (3)	-	-
Headache	7 (6)	7 (6)	9 (9)	8 (8)	13 (7)	15 (8)	3 (3)	10 (9)
Nasopharyngitis	9 (8)	4 (4)	9 (9)	7 (7)	27 (14)	39 (20)	3 (3)	4 (4)
Upper respiratory tract infection	7 (6)	6 (5)	2 (2)	6 (6)	7 (4)a	7 (4)a	2 (2)	3 (3)
Pharyngitis	5 (4)	2 (2)	1 (<1)	0	2 (1)	6 (3)	-	-
Sinusitis	4 (4)	2 (2)	2 (2)	3 (3)	7 (4)	4 (2)	-	-
Hypersensitivity	■ (■)	■ (■)	NR	NR	■ (■)	■ (■)	NR	NR
Cough	1 (<1)	3 (3)	2 (2)	2 (2)	6 (3)	13 (7)	-	-
Oropharyngeal pain	3 (3)	3 (3)	2 (2)	3 (3)	8 (4)	7 (4)	2 (2)c	4 (4)c
Oropharyngeal candidiasis	3 (3)	1 (<1)	3 (3)b	3 (3)b	1 (<1)	2 (1)	4 (4)	4 (4)
Bone disorders	■ (■)	■ (■)	NR	NR	■ (■)	■ (■)	NR	NR
Diarrhoea	1 (<1)	3 (3)	4 (4)	1 (1)	-	-	-	-
Cardiovascular effects	■ (■)	■ (■)	NR	NR	■ (■)	■ (■)	NR	NR
Abdominal pain	-	-	3 (3)	1 (1)	-	-	-	-
Dysphonia	-	-	1 (<1)	4 (4)	2 (1)	4 (2)	4 (4)	2 (2)
Influenza	-	-	-	-	8 (4)	7 (4)	1 (1)	0
Rhinitis	-	-	0	0	2 (1)	7 (4)	-	-

<sup>a</sup> Respiratory tract infection viral; <sup>b</sup> Oral candidiasis; <sup>c</sup> Pharyngolaryngeal pain

Abbreviations: NR = not reported

Source: Table 31, p99 of the submission and table 34, p102-103 of the submission

- 6.14 Overall, the rate of adverse events across the four trials in patients treated with FF compared to patients treated with FP appears to be similar. Additional data on potential safety concerns beyond those identified in the clinical trials, including data from seven additional studies in which patients were treated with FF, were also provided. Overall there is no evidence to suggest that FF has a significantly different safety profile to other ICS currently used in the maintenance of asthma.

### Clinical claim

- 6.15 The submission describes FF as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over FP. The evaluation considered that the claim of non-inferiority in efficacy may not be adequately supported as three of the four trials identified were not powered to detect non-inferiority between FP and FF. Although, the results do suggest that there is no statistically significant difference in change from baseline through FEV1 in patients treated with FP and FF and both therapies are superior to placebo. The ESC considered that the efficacy data were consistent with a claim of non-inferiority. The claim of non-inferiority in safety is reasonably supported by the available data, however the availability of data for long

term treatment with FF is limited as it has only been marketed internationally for a short period of time.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

**Economic analysis**

- 6.16 The submission presents a cost minimisation analysis against FP only.
- 6.17 Based on clinical trials, the equi-effective doses are estimated as FF 100mcg once daily is equivalent to FP 250mcg twice daily, and FF 200mcg once daily is equivalent to FP 500mcg twice daily. The submission also implicitly assumes that FF 100mcg can substitute for, and therefore is equivalent to, other mid-dose ICS including beclomethasone 200mcg twice daily, budesonide 400mcg twice daily and ciclesonide 160mcg twice daily. The ESC supported the assumption that FF 100mcg was equivalent to other mid-dose ICS.
- 6.18 The submission presents a DPMQ of \$ [REDACTED] for FF 100mcg, 30 doses (1 month’s supply) and \$ [REDACTED] for FF 200mcg, 30 doses (1 month’s supply). The price for FF is equivalent to FP at the appropriate dose. The PSCR (p5) maintains that the cost-minimisation against FP alone was the most appropriate comparison on which to base an economic evaluation.

**Drug cost/patient/year: \$ [REDACTED] to \$ [REDACTED]**

- 6.19 The drug cost for FF and other PBS listed ICSs per year are summarised in Table 7.

**Table 7: Drug cost for FF and other PBS listed ICSs per year**

Drug	Cost/year	Assumptions
Mid-dose ICS		
FF 100mcg, 30	\$ [REDACTED]	12 scripts/year
FP 250mcg, 60	\$ [REDACTED]	
Beclomethasone 100mcg, 200	\$ [REDACTED]	8 scripts/year
Beclomethasone 100mcg autoinhaler, 200	\$ [REDACTED]	8 scripts/year
Budesonide 400mcg, 200	\$ [REDACTED]	4 scripts/year
Ciclesonide 160mcg, 120	\$ [REDACTED]	6 scripts/year
High-dose ICS		
FF 200mcg, 30	\$ [REDACTED]	12 scripts/year
FP 500mcg, 60	\$ [REDACTED]	

- 6.20 The ESC considered that in practice, patients may inappropriately use FF more than once daily, resulting in an increased cost per patient per year.

**Estimated PBS usage & financial implications**

- 6.21 This submission was not considered by DUSC. The submission uses a market share approach to estimate the financial impact of listing FF on the PBS. The main source of market share data is from PBS statistics from January 2014 to December 2014, as well as a 10% PBS sample. The estimated uptake rate for FF is based on the uptake rate of ciclesonide (the most recent PBS listed ICS) in the first 5 years of listing on the PBS.

**Table 8: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated extent of use</b>					
Number treated					
Uptake rate	6%	10%	12%	14%	16%
Actual uptake rate <sup>1</sup>	5.76%	9.59%	11.51%	13.43%	15.35%
FF 100mcg					
FF 200mcg					
Total <sup>2</sup>					
<b>Estimated net cost to PBS/RPBS/MBS</b>					
Net cost to PBS/RPBS	-\$	-\$	-\$	-\$	-\$
Net cost to MBS <sup>3</sup>	0	0	0	0	0
<b>Estimated total net cost</b>					
<b>Net cost to PBS/RPBS/MBS</b>	<b>-\$</b>	<b>-\$</b>	<b>-\$</b>	<b>-\$</b>	<b>-\$</b>

Source: Section E workbook.xlsx

*Text in italics indicate values calculated during evaluation*

<sup>1</sup> As discussed in section E.1 of the commentary, the submission's assumption of 32.51% FF 100mcg and 63.40% FF 200mcg is arithmetically inaccurate as it does not add up to 100%, leading to an uptake rate lower than what has been claimed by the submission

<sup>2</sup> Minor discrepancies in totals due to rounding in spreadsheet. Not expected to change outcomes to any appreciable degree.

<sup>3</sup> No cost to MBS or state government budgets expected.

The redacted table above shows that at year 5, the estimated number of patients treated with fluticasone furoate was 50,000 – 100,000 per year at a net saving of less than \$10 million per year.

6.22 The evaluation considered the base case financial estimates presented:

- are likely an underestimate (i.e. savings are unrealistic) as the estimates are driven by the substitution of mid-dose ICS by FF 100mcg. However, the submission's assumption that one FF dispensing (containing one month's supply) will replace one other ICS dispensing is unreasonable as the number of doses in beclomethasone, ciclesonide and budesonide all exceed one month's supply.;
- are likely to be inaccurate as the copayment is likely to be overestimated since the submission assumes that general patients will pay \$37.70, which is implausible as the DPMQ for FP 250mcg, 60 doses, is \$31.50 and the submission's estimate for FF is based on FP;
- are likely to be inaccurate as the number of substitution in the mid-dose ICS relative to high-dose ICS is underestimated – PBS data shows more mid-dose ICS than high-dose ICS are dispensed (54.7% vs 21.93% of all PBS scripts in Jan-Dec 2014, a ratio of greater than 2:1) but the submission assumes the reverse; that more patients will use high-dose FF 200mcg compared to the mid-dose FF 100mcg at a reverse ratio of about 2:1 (63.4% for FF 200mcg vs 32.51% of FF 100mcg)
- inappropriately assumes that only 77.8% of patients on the RPBS are greater than 12 years of age. Given the conditions for eligibility for RPBS it is unlikely there are many patients who received a RPBS script would not be an adult;

6.23 A range of sensitivity analyses were presented by the submission and conducted during the evaluation (see Table 9).

**Table 9: Sensitivity analysis conducted during evaluation**

<b>Scenario 1: Method to calculate substitution (base case: estimate annual uptake across all ICS then multiply by assumed FF100/200 split; scenario 1: apply annual uptake to mid-dose (substituting for FF100) and high-dose ICS (substituting for FF200) separately based on Jan-Dec 2014 PBS proportion and annual growth of 1.13%)</b>					
<b>Number of packs</b>					
<i>Base case</i>	<b>Year 1</b>	<b>Year 2</b>	<b>Year 3</b>	<b>Year 4</b>	<b>Year 5</b>
FF100					
FF200					
Total					
<i>Scenario 1</i>					
FF100					
FF200					
Total					
<b>Net Cost</b>					
Base case	-\$	-\$	-\$	-\$	-\$
Scenario 1	-\$	-\$	-\$	-\$	-\$
<b>Scenario 2: As per scenario 1, plus adjusting for script equivalence</b>					
<b>Net Cost</b>					
Base case	-\$	-\$	-\$	-\$	-\$
Submission's sensitivity for script equivalence	\$	\$	\$	\$	\$
Scenario 2	\$	\$	\$	\$	\$

Source: constructed during evaluation

The redacted table above shows that at year 5, under Scenario 1, the net cost would be less than \$10 million, and under Scenario 2, the net cost would be less than \$10 million.

- 6.24 The estimates are most sensitive to the changes around the assumption of script equivalence.

**Quality Use of Medicines**

- 6.25 The submission has outlined a plan to work with clinicians to ensure that FF is only used in patients aged 12 years or over until such time that relevant clinical data is available. A Risk Management Plan to this effect has been submitted to the TGA.
- 6.26 The submission has not addressed the potential quality use of medicine issue that given there are only two doses of FF, that the 100mcg and 200mcg presentations may be interpreted to be low- and mid-dose ICS, rather than the proposed mid- and high-dose preparations, respectively. The PSCR (p2) highlighted that this is addressed in the Product Information for FF/VI.

**Other matters**

- 6.27 The submission and the PSCR (p5) requested that the PBS legislative instrument (PB71 of 2012) be amended for all FP and FF containing products to reflect the active molecule (i.e. differentiate between fluticasone propionate and fluticasone furoate) instead of the listed drug being fluticasone only as the two are structurally distinct drugs with different pharmacological and physicochemical properties.

- 6.28 Drugs are declared to be pharmaceutical benefits under Section 85(2) of the *National Health Act 1953* (Act). Section 85(3) of the Act provides for the Minister to determine, by reference to strength, type of unit, size of unit or otherwise, the form or forms of a listed drug. These details, among others, are captured in the *National Health (Listing of Pharmaceutical Benefits) Instrument* (currently PB71 of 2012), which is updated on the 1<sup>st</sup> of each month to reflect any new or amended PBS listings.
- 6.29 Table 10 below provides the *National Health (Listing of Pharmaceutical Benefits) Instrument* entries for all fluticasone containing medicines. In all cases, the 85(2) drug is currently declared as fluticasone, with the ester (propionate or furoate) defined as part of the form. The sponsor requested the PBAC advice the Minister that fluticasone propionate and fluticasone furoate should be declared as different s85(2) drugs for the purposes of the *National Health Act 1953*.

**Table 10: National Health (Listing of Pharmaceutical Benefits) instrument entries for fluticasone**

85(2) Drug	85(3) Form	Brand Name	Responsible Person
Fluticasone	Powder for oral inhalation in breath actuated device containing fluticasone propionate 100 micrograms per dose, 60 doses	Flixotide Junior Accuhaler	GlaxoSmithKline Australia Pty Ltd
Fluticasone	Powder for oral inhalation in breath actuated device containing fluticasone propionate 250 micrograms per dose, 60 doses	Flixotide Accuhaler	GlaxoSmithKline Australia Pty Ltd
Fluticasone	Powder for oral inhalation in breath actuated device containing fluticasone propionate 500 micrograms per dose, 60 doses	Flixotide Accuhaler	GlaxoSmithKline Australia Pty Ltd
Fluticasone	Pressurised inhalation containing fluticasone propionate 125 micrograms per dose, 120 doses (CFC-free formulation)	Flixotide	GlaxoSmithKline Australia Pty Ltd
Fluticasone	Pressurised inhalation containing fluticasone propionate 250 micrograms per dose, 120 doses (CFC-free formulation)	Flixotide	GlaxoSmithKline Australia Pty Ltd
Fluticasone	Pressurised inhalation containing fluticasone propionate 50 micrograms per dose, 120 doses (CFC-free formulation)	Flixotide Junior	GlaxoSmithKline Australia Pty Ltd
Fluticasone with eformoterol	Pressurised inhalation containing fluticasone propionate 125 micrograms with eformoterol fumarate dihydrate 5 micrograms per dose, 120 doses	flutiform 125/5	Mundipharma Pty Limited
Fluticasone with eformoterol	Pressurised inhalation containing fluticasone propionate 250 micrograms with eformoterol fumarate dihydrate 10 micrograms per dose, 120 doses	flutiform 250/10	Mundipharma Pty Limited
Fluticasone with eformoterol	Pressurised inhalation containing fluticasone propionate 50 micrograms with eformoterol fumarate dihydrate 5 micrograms per dose, 120 doses	flutiform 50/5	Mundipharma Pty Limited
Fluticasone with salmeterol	Powder for oral inhalation in breath actuated device containing fluticasone propionate 100 micrograms with salmeterol 50 micrograms (as xinafoate) per dose, 60 doses	Seretide Accuhaler 100/50	GlaxoSmithKline Australia Pty Ltd
Fluticasone with	Powder for oral inhalation in breath actuated device	Seretide	GlaxoSmithKline

85(2) Drug	85(3) Form	Brand Name	Responsible Person
salmeterol	containing fluticasone propionate 250 micrograms with salmeterol 50 micrograms (as xinafoate) per dose, 60 doses	Accuhaler 250/50	Australia Pty Ltd
Fluticasone with salmeterol	Powder for oral inhalation in breath actuated device containing fluticasone propionate 500 micrograms with salmeterol 50 micrograms (as xinafoate) per dose, 60 doses	Seretide Accuhaler 500/50	GlaxoSmithKline Australia Pty Ltd
Fluticasone with salmeterol	Pressurised inhalation containing fluticasone propionate 125 micrograms with salmeterol 25 micrograms (as xinafoate) per dose, 120 doses (CFC-free formulation)	Seretide MDI 125/25	GlaxoSmithKline Australia Pty Ltd
Fluticasone with salmeterol	Pressurised inhalation containing fluticasone propionate 250 micrograms with salmeterol 25 micrograms (as xinafoate) per dose, 120 doses (CFC-free formulation)	Seretide MDI 250/25	GlaxoSmithKline Australia Pty Ltd
Fluticasone with salmeterol	Pressurised inhalation containing fluticasone propionate 50 micrograms with salmeterol 25 micrograms (as xinafoate) per dose, 120 doses (CFC-free formulation)	Seretide MDI 50/25	GlaxoSmithKline Australia Pty Ltd
Fluticasone with vilanterol	Powder for oral inhalation in breath actuated device containing fluticasone furoate 100 micrograms with vilanterol 25 micrograms (as trifenate) per dose, 30 doses	Breo Ellipta 100/25	GlaxoSmithKline Australia Pty Ltd
Fluticasone with vilanterol	Powder for oral inhalation in breath actuated device containing fluticasone furoate 200 micrograms with vilanterol 25 micrograms (as trifenate) per dose, 30 doses	Breo Ellipta 200/25	GlaxoSmithKline Australia Pty Ltd

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

## 7 PBAC Outcome

- 7.1 The PBAC recommended the listing of fluticasone, in the form fluticasone furoate (FF), as an unrestricted benefit. The PBAC recommended listing on a cost-minimisation basis to existing inhaled corticosteroid (ICS) monotherapy fluticasone, in the form of fluticasone propionate (FP). The equi-effective doses were considered to be FF 100 microgram once daily and FP 250 microgram twice daily, and FF 200 microgram once daily and FP 500 microgram twice daily.
- 7.2 The PBAC considered that FP, beclomethasone, ciclesonide and budesonide were all relevant comparators. The PBAC also recalled that FP and ciclesonide have previously been considered non-inferior, and that FP has been considered superior to both beclomethasone and budesonide (Therapeutic Relativity Sheets, June 2015). The PBAC considered that on this basis, the submission's approach of comparing FF against FP alone was reasonable.
- 7.3 The PBAC considered that the claim of non-inferior comparative effectiveness and safety compared to FP was reasonable.

- 7.4 The PBAC considered the sponsors request that the PBAC advise the Minister that FF and FP should be declared as different drugs under section 85(2) of the Act. The PBAC noted the different pharmacology and physicochemical properties of FP and FF and that these resulted in FP and FF having different doses and dosing regimens in clinical practice. However, the PBAC also noted that the outcomes of treatment with FP and FF are not different and on this basis considered it appropriate for FP and FF to continue to be determined as forms of the drug fluticasone for the purposes of the Act.
- 7.5 In accordance with subsection 101(3BA) of the *National Health Act* 1953, the PBAC advised that it is of the opinion that fluticasone should be treated as interchangeable on an individual patient basis with ciclesonide.
- 7.6 The PBAC advised that fluticasone is suitable for prescribing by nurse practitioners.
- 7.7 The PBAC recommended that the Safety Net 20 Day Rule should apply.

**Outcome:**

Recommended

**8 Recommended listing**

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
FLUTICASONE			Arnuity® Ellipta®	GSK
Fluticasone furoate 100 microgram/actuation inhalation: powder for, 30 actuations	1	5		
Fluticasone furoate 200 microgram/actuation inhalation: powder for, 30 actuations	1	5		

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	-
<b>Severity:</b>	-
<b>Condition:</b>	-
<b>PBS Indication:</b>	-
<b>Treatment phase:</b>	-
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	-

<b>Administrative Advice</b>	-
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**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**

The sponsor had no comment.