

7.03 FLUTICASONE FUROATE, Powder for Inhalation, 100 mcg and 200 mcg, Arnuity® Ellipta®, GlaxoSmithKline.

1 Purpose of Application

1.1 The resubmission requested that:

- Fluticasone furoate (FF) (brand name: Arnuity® Ellipta®* be declared a ‘drug’ for the purpose of section 85(2) of the *National Health Act 1953* (Cth) (‘the Act’); and
- The listing instruments for each of Breo® Ellipta®†, Seretide® and Flixotide® be amended to reflect the name of the active moiety of the respective inhaled corticosteroid (ICS) component of each product, being FF in the case of Breo® Ellipta® and fluticasone propionate (FP) in the case of both Seretide® and Flixotide® (see Table 1).

Table 1: Proposed amendments to the listing instruments

Brand name	Listed drug name	
	Current listing instrument	Proposed listing instrument
Breo® Ellipta®	Fluticasone with vilanterol	Fluticasone furoate with vilanterol
Seretide®	Fluticasone with salmeterol	Fluticasone propionate with salmeterol
Flixotide®	Fluticasone	Fluticasone propionate

Source: Table 1, p19 of the resubmission

Approach taken by the resubmission

1.2 In support of the requests, the resubmission included the following information:

- Section A: provided background information relating to the issues of the listing instruments for the purposes of the Act.
- Section B: presented evidence (structural profile, pharmacological data, expert opinion etc.) to claim that FF and FP are distinct ‘drugs’.
- Section C: argued that the non-inferiority of FF versus FP (accepted by PBAC following the previous submission) is irrelevant to the question of whether FF and FP are the same ‘drug’.

Approach taken by the Commentary

1.3 The main body of the Commentary focused on appraising the scientific evidence presented primarily in Section B of the resubmission and discussed differences/similarities between FF and FP in terms of physicochemical characteristics, pharmacokinetics, and pharmacodynamics.

1.4 It was beyond the scope of the evaluation to address the information provided in the resubmission regarding the naming conventions for drugs as they may relate to the Act. This information has been summarised in the Background.

* Arnuity® Ellipta®: Arnuity® refers to the fluticasone furoate drug product, and Ellipta® is the inhalation device.

† Breo® Ellipta®: Breo® refers to the drug combination product of fluticasone furoate and vilanterol, and Ellipta® is the inhalation device.

2 Requested listing

- 2.1 The listing of fluticasone, in the form fluticasone furoate, as an unrestricted benefit was recommended by the PBAC (5.07 Fluticasone PSD, November 2015 PBAC meeting). The current resubmission did not propose a change to the PBS restriction, but requested that fluticasone furoate be declared a 'drug' (not as a form of fluticasone) for the purpose of the Act.

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

3 Background

- 3.1 Fluticasone furoate was listed on the ARTG in September 2015 for the maintenance treatment of asthma in patients aged ≥ 12 years.
- 3.2 This was the second FF submission to the PBAC. At the November 2015 meeting, the PBAC recommended the listing of fluticasone, in the form fluticasone furoate, as an unrestricted benefit, on a cost-minimisation basis to fluticasone in the form of fluticasone propionate. The equi-effective doses were considered to be FF 100 micrograms (mcg) once daily and FP 250 mcg twice daily. The PBAC considered the claim of non-inferior comparative effectiveness and safety compared with FP was reasonable.
- 3.3 The previous FF submission also requested that the PBAC advise the Minister that FF and FP should be declared as different drugs under Section 85(2) of the Act. At the November 2015 meeting, the PBAC noted the different pharmacology and physicochemical properties of FP and FF and that these resulted in FP and FF having different dosing regimens in clinical practice. However, the PBAC considered it appropriate for FP and FF to continue to be determined as forms of the drug fluticasone for the purposes of the Act.
- 3.4 In 2007, the *National Health Act 1953* was amended by the *National Health Amendment (Pharmaceutical Benefits Scheme) Act 2007 (Cth)* (amending Act). The Explanatory Statement relating to the legislative amendment¹ noted that:

"The descriptions of drugs in the Schedules have been revised to refer, where appropriate, to the active moiety.

The Schedules to the instrument now refer to "Listed Drug" and not "Pharmaceutical Benefit" since the pharmaceutical benefit in most cases will be the pharmaceutical item composed of the listed drug in a particular form and with a particular manner of administration".

- 3.5 As part of the wider reform, terminology in existing listing instruments was amended to ensure consistency with changes introduced by the amending Act. The listing instruments for Flixotide[®] and Seretide[®] were amended, changing Column 1 from 'Name of pharmaceutical benefit' to 'Listed Drug' and changing the name of FP to 'fluticasone' in that column with reference to 'fluticasone propionate' under the column purportedly as the form of the drug (Instrument PB 71 of 2012). Subsequently, in December 2014, FF as a combination therapy with vilanterol under

the brand name Breo[®] Ellipta[®] was recognised as ‘fluticasone with vilanterol’ in the listing instrument under Column 1 titled ‘Listed Drug’, ‘fluticasone furoate’ is the form of the drug fluticasone for the purposes of the Act (Instrument PB 71 of 2012).

3.6 The resubmission noted that:

- It was the sponsor’s understanding that the Department referenced the Anatomical Therapeutic Chemical (ATC) classification system when it determined the classification of all drug names. FP and FF have different ATC names: ‘fluticasone’ and ‘fluticasone furoate’, respectively;
- The sponsor was recently informed that the WHO International Non-proprietary Names (INN) list could be used as an externally sourced, independent guide to the naming of ‘drugs’ on the PBS. The ‘fluticasone’ INN was granted based on clinical and pharmacological data relating to fluticasone propionate. ‘Fluticasone furoate’ was granted a separate INN;
- The TGA designated FF as a new chemical entity status when it evaluated the application of Avamys[®];
- The European Medicines Agency stated that FF is not a salt or prodrug; the entire molecule is required for pharmacological activity. FF is not metabolised to fluticasone, i.e. the furoate ester is an integral part of the respective medicinal entity and remains covalently bound to the fluticasone steroid backbone (European Public Assessment Report for Avamys[®]);
- There was expert opinion that FF and FP are different drugs and not forms of the drug ‘fluticasone’.

3.7 The resubmission argued that all the above points provide support for the request that ‘fluticasone propionate’ and ‘fluticasone furoate’ should be declared as different s85(2) drugs for the purposes of the Act.

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

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 ICSs are effective preventer medicines for asthma.

4.2 FF and FP are synthetic trifluorinated corticosteroids (specifically, glucocorticoids). Corticosteroids diffuse across cell membranes and bind to glucocorticoid receptors in the cytoplasm of target cells. This binding creates an activated glucocorticoid-receptor-corticosteroid complex that translocates across the nuclear membrane and binds to DNA sequences, affecting gene transcription and protein synthesis. By modifying the production of mediators of inflammation in the airways in different cell types (e.g. eosinophils and macrophages), corticosteroids reduce airway inflammation and hyper-responsiveness. The mechanism of action of FF and FP in their respective product information (PI) documents is the same.

4.3 FF is indicated for the maintenance treatment of asthma in patients aged ≥12 years and is administered once daily. FP is indicated for the prophylactic management of

asthma in adults and children of ages 1 year and older and is administered twice daily.

- 4.4 The starting dose for FF is typically 100 mcg daily, with a recommended dose between 100 mcg and 200 mcg daily, depending on asthma severity. The starting dose for FP is typically 100 mcg twice daily, with a recommended dose between 100 mcg and 1000 mcg, twice daily (in adults), depending on asthma severity. To minimise adverse reactions, ICSs should be used at the lowest dose that maintains symptom control. Dosing information is based on the respective PI documents. The resubmission did not provide evidence or data for doses used in clinical practice. Relevant data on the usual and maximum doses of FF and FP that are used in clinical practice were not found during the evaluation.

5 Comparator

- 5.1 The previous submission nominated FP as the appropriate comparator. This was accepted by the PBAC (paragraph 7.2, 5.07 Fluticasone PSD, November 2015 PBAC meeting). However, the choice of comparator is not relevant to the current submission.

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.

Evidence presented in the resubmission

- 6.3 Studies cited in the resubmission addressed physicochemical characteristics, pharmacodynamic properties and pharmacokinetic properties of FF and FP. The search strategies and results of the searches were not provided in the resubmission. A list of studies included in the resubmission was not provided, however studies cited in the resubmission were retrieved and reviewed during the evaluation.
- 6.4 Relevant study information was sourced from individual published papers during the evaluation and is summarised in Table 2 below.

Table 2: Overview of the studies presented in the re-submission

Study	Affiliation	Description of the study	Outcomes
FF versus FP			
Biggadike 2008 ⁸	GSK	NA	Physicochemical characteristics: - X-ray crystallography structures of the glucocorticoid-receptor-corticosteroid complexes for FF and FP

Public Summary Document – March 2017 PBAC Meeting

Study	Affiliation	Description of the study	Outcomes
Rossios 2011 ⁹	GSK	- Cells from COPD and asthma patients, and cells from healthy volunteers (all PBMC cells) - Respiratory cell lines (A549, H ₂ O ₂ -treated A549, BEAS2B)	Pharmacodynamics: - Inhibition of the release of inflammatory proteins - Activity under oxidative-stress conditions
Salter 2007 ¹⁰	GSK	- Human respiratory cellular assays - Animal model ^a	Pharmacodynamics: - Anti-inflammatory activity - Maintenance of epithelial cell barriers - Retention in, and transport across, respiratory tissue - Pharmacodynamic effects on downstream receptor pathways
Valotis 2007 ¹¹	GSK ^b	- Human lung tissue samples from patients with bronchial carcinoma (cancer-free tissue) - Plasma sample from healthy volunteers	Pharmacodynamics: - Glucocorticoid-receptor-corticosteroid interactions - Lung tissue binding affinity
Allen 2013 ¹²	GSK	Open-label, part-randomised, crossover study in healthy male subjects (n=24)	Pharmacokinetics: - Absorption - Elimination
FF only			
Hughes 2008 ¹³	GSK	Open-label, crossover study in healthy male subjects (n=5)	Pharmacokinetics: - Metabolism
Biggadike 2006 ¹⁴	GSK	NA	Physicochemical characteristics: - X-ray crystallography structure of the glucocorticoid-receptor-corticosteroid complex for FF
FP only			
Falcoz 2000 ¹⁵	GSK	Double-blinded, randomised, placebo-controlled study in patients with mild-to-moderate asthma (n=232 in Study 1) ^c	Pharmacokinetics: - Absorption
Falcoz 2000 ¹⁵	GSK	Double-blinded, randomised, placebo-controlled study in patients with mild-to-moderate asthma (n=212 in Study 2) ^c	Pharmacokinetics: - Absorption
Pearce 2006 ¹⁶	Various ^d	- Microsome preparations from human liver donors - Human pulmonary microsomes prepared from surgical specimens of lung tissue from donors - Insect cells, microsomes	Pharmacokinetics: - Metabolism

FF = fluticasone furoate; FP = fluticasone propionate; NA = not applicable; PBMC = peripheral blood mononuclear cells

^a Only for assessment of the anti-inflammatory activity

^b Parts of this study were supported by a research grant of GSK. This funding had no role in the collection, analysis and interpretation of data or in the writing of the manuscript.

^c This paper reported results of two studies. The first study compared 2 dosages of FP administered via the Diskhaler[®]; the second compared one FP dosage administered via the Diskhaler[®] and the Diskus[®].

^d This work was supported in part by grants from the Pediatric Pharmacology Research Unit Network and Pediatric Adverse Drug Reaction Network, National Institute of Child Health and Human Development, Bethesda, MD, and by a grant from the Katherine Berry Richardson Foundation, Children's Mercy Hospital, Kansas City, MO.

Source: Table compiled during the evaluation on the basis of the study information provided in the published papers.

Physicochemical characteristics

- 6.5 FF and FP are structurally related but they differ in the ester moiety attached to the 17- α position on the right side of each molecule.
- 6.6 X-ray crystallography structures of the glucocorticoid-receptor-corticosteroid complexes found that the 17- α ester groups of both FF and FP bind to the receptor via a lipophilic pocket (17- α pocket) that can contain these functional groups. The propionate group of FP only partially fills this pocket, enabling considerable freedom of movement and relatively weaker binding compared with the larger furoate ester group of FF. The resubmission claimed that these crystal structure complexes provide evidence that the intact forms of FF and FP are necessary to bind to the receptor and exert a therapeutic effect. The *PBAC* noted that the furoate and propionate esters influenced the binding characteristics of FF and FP.

Pharmacodynamics

- 6.7 A summary of the differences between FF and FP in the pharmacodynamic effects reported is in Table 3. These differences are discussed below.

Table 3: Summary of differences between FF and FP in pharmacodynamic effects

	FF	FP	Statistically significant	Source
Glucocorticoid-receptor-corticosteroid interactions^a				
Receptor binding affinity: relative receptor affinity ^b , RRA	2989 (\pm 135) ^c	1775 (\pm 130) ^c	P<0.001	Valotis 2007
Receptor binding kinetics: association rate constants ^c , $k_1 \times 10^5$	37.46 (\pm 0.73) L/[mol/min]	21.17 (\pm 0.56) L/[mol/min]	P \leq 0.001	Valotis 2007
Receptor binding kinetics: dissociation rate constants ^d , K_D	0.30 (\pm 0.02) nmol/L	0.51 (\pm 0.03) nmol/L	No ^h	Valotis 2007
Lung tissue binding affinity	4.18 (\pm 0.16) ng/mg	3.39 (\pm 0.06) ng/mg	P \leq 0.001	Valotis 2007
Inhibition of the release of inflammatory proteins^e				
Inhibition of release of GM-CSF in A549 cells, IC ₅₀ value	0.009 nM	0.016 nM	NR	Rossios 2011
Inhibition of release of CXCL8 in A549 cells, IC ₅₀ value	0.063 nM	0.11 nM	NR	Rossios 2011
Inhibition of release of GM-CSF in BEAS2B cells, IC ₅₀ value	0.002 nM	0.005 nM	NR	Rossios 2011
Inhibition of release of CXCL8 in BEAS2B cells, IC ₅₀ value	0.014 nM	0.024 nM	NR	Rossios 2011
Activity under oxidative-stress conditions^e				
Inhibition of release of CXCL8/IL8 in PBMCs of COPD patients, IC ₅₀ value	3.9 (\pm 1.7) nM	184.3 (\pm 130.2) nM ^f	No (P=0.057)	Rossios 2011
Inhibition of release of CXCL8/IL8 in PBMCs of healthy subjects, IC ₅₀ value	14.2 (\pm 8.0) nM	6.0 (\pm 1.3) nM	NR	Rossios 2011
Inhibition of release of CXCL8/IL8 in PBMCs of asthma patients, IC ₅₀ value	1.9 (\pm 0.64) nM	4.0 (\pm 1.6) nM	No (P=0.34)	Rossios 2011
Inhibition of release of GM-CSF in H ₂ O ₂ -treated A549 cells, IC ₅₀ value	0.064 nM	1.2 nM	NR	Rossios 2011
Inhibition of release of GM-CSF in non-H ₂ O ₂ -treated A549 cells, IC ₅₀ value	0.016 nM	0.034 nM	NR	Rossios 2011
Maintenance of epithelial cell barriers^g				
Activation of the GRE pathway in human respiratory cellular assays, pEC ₅₀ \pm SD value	10.24 (\pm 0.07)	10.13 (\pm 0.26)	No ^h	Salter 2007
Pharmacodynamic effects on downstream receptor pathways^f				
Inhibition of the transcription of pro-inflammatory gene products by NF- κ B, pEC ₅₀ \pm SD value	10.53 (\pm 0.27)	10.36 (\pm 0.34)	P<0.001	Salter 2007

COPD = chronic obstructive pulmonary disease; FF = fluticasone furoate; FP = fluticasone propionate; GM-CSF, CXCL8/IL8, CXCL8 = inflammatory proteins; GRE = glucocorticoid response elements; H₂O₂ = hydrogen peroxide; NF- κ B = a pro-inflammatory nuclear transcription factor; NR = not reported; PBMC = peripheral blood mononuclear cell; SD = standard deviation

^a Values are means and mean deviations of the means.

^b RRA expressed relative to the standard of dexamethasone, which has a RRA of 100.

^c Mean and mean deviation of the mean of three to seven experiments.

^d The binding (association) and unbinding (dissociation) between the inhaled corticosteroid and the glucocorticoid receptor.

^e The IC₅₀ value, a measure of potency, represents the mean concentration of glucocorticoid required to inhibit the synthesis or release of inflammatory mediators by 50 percent. Values are means and standard errors of the means.

^f This IC₅₀ value for FP of 184.3 (\pm 130.2) nM was also reported in the same study (Rossios 2011) as 192.6 (\pm 125.5) nM.^g pEC₅₀ \pm SD (standard deviation), a measure of potency, is the negative of the log of the mean molar concentration that produces 50 percent of the maximum possible response.

^h Actual P value not reported.

Source: Table compiled during the evaluation

- 6.8 FF had a higher relative receptor affinity and faster association rate constant for the lung glucocorticoid receptor, and a higher lung tissue binding affinity, compared to FP. A higher receptor-binding affinity of an ICS could indicate a more potent and prolonged anti-inflammatory activity, but could also be associated with an increased risk of systemic adverse effects. A higher affinity for lung tissue may prolong pulmonary residence time, increase the duration of anti-inflammatory effects, and reduce the risk of systemic exposure. Greater potency could mean that a lower dose of the ICS will be required to occupy the same number of glucocorticoid receptors in the lungs, leading to the requirement of a lower daily dose for equivalent efficacy. For some pharmacodynamic parameters, the potency of FF was higher than for FP.
- 6.9 Evidence for the impact on clinical effectiveness or safety due to differences in pharmacodynamic effects between FF and FP was neither provided by the resubmission nor found during the evaluation. The PBAC recalled that they previously considered that FF is non-inferior to FP in terms of safety and efficacy.

Pharmacokinetics

- 6.10 A summary of the differences between FF and FP in the pharmacokinetic parameters reported is in Table 4. These differences are discussed below.

Table 4: Summary of differences between FF and FP in pharmacokinetic parameters

	FF	FP	Source
Absorption			
Oral bioavailability	1.3%	0.91%	FF: Arnuity Ellipta TGA-approved PI; FP: Falcoz 2000
Pulmonary bioavailability	6.3% to 18.4%	9%	Allen 2013
Pulmonary residence time, MAT	7 hours	2.1 hours	Allen 2013
Pulmonary residence time, T90	19 hours to 32 hours	11 hours	Allen 2013
Distribution			
Volume of distribution	661 L/kg	300 L/kg	FF: Arnuity Ellipta TGA- and FDA-approved PIs; FP: Flixotide TGA-approved, and Flovent HFA FDA-approved, PIs
Protein binding	99.6%	91%	FF: Arnuity Ellipta TGA- and FDA-approved PIs; FP: Flixotide TGA-approved, and Flovent HFA FDA-approved, PIs
Systemic clearance	NA	66 L/hour	FP: Flixotide TGA-approved, and Flovent HFA FDA-approved, PIs
Elimination			
Terminal elimination half-life: inhaled administration	17 to 24 hours	11 hours	Allen 2013
Terminal elimination half-life: intravenous administration	14 hours	14 hours	Allen 2013

FF = fluticasone furoate; FDA = Food and Drug Administration; FP = fluticasone propionate; MAT = mean absorption time, mean time necessary for a drug molecule to be absorbed from the lungs into the systemic circulation; NA = not available (estimate not found during the evaluation); T90 = time for 90 percent of the drug to be absorbed, calculated from the terminal pulmonary half-life after inhalation, this relates to the pulmonary residence time. Source: Table compiled during the evaluation

- 6.11 Oral bioavailability was low for FF and slightly lower for FP (due to extensive first-pass metabolism) although pulmonary bioavailability was similar. Pulmonary bioavailability of an ICS is important for drug efficacy, while both the pulmonary and orally absorbed fractions of an ICS may contribute to the risk of adverse effects. The MAT and T90 estimates indicated that FF had a longer pulmonary residence time, or was more slowly absorbed from the lungs into the systemic circulation, compared to FP. Increased pulmonary retention or a slower absorption out of the lungs of an ICS results in a longer duration of action and may permit less frequent dosing.
- 6.12 FF had a larger volume of distribution than FP, however the impact of this on the efficacy of either drug is uncertain.
- 6.13 FF had a longer elimination half-life compared to FP following inhaled administration, however duration of effect may be more closely related to pulmonary half-life, which was not reported in the resubmission.
- 6.14 The resubmission stated that FF and FP do not have common metabolites and that their metabolites are substantially less active than the parent molecule. This was supported by the literature.

Conclusion

- 6.15 The resubmission provided evidence of differences in the physicochemical profiles, pharmacodynamics and pharmacokinetics between FF and FP. The pharmacodynamic and pharmacokinetic differences presented tend to support the claim that different dosing regimens of FF and FP may be required to achieve the same clinical endpoint.
- 6.16 The PBAC recalled its previous recommendation that FF and FP were non-inferior in terms of comparative safety and efficacy, and therefore considered that any pharmacodynamic and pharmacokinetic differences between FF and FP did not result in any significant differences in safety, efficacy, or health outcomes.
- 6.17 The PBAC considered that, on balance, the evidence presented in the submission supported the claim that the furoate and propionate esters of fluticasone influenced the pharmacodynamic and pharmacokinetic properties of FF and FP such that they could be considered different 'active moieties' and should therefore be declared as different drugs for the purposes of section 85(2) of the National Health Act 1953 (the Act).

The PBAC noted that "if the Committee is of the opinion that a drug or medicinal preparation should be made available as a pharmaceutical benefit under this Part, the Committee must, in its recommendation under subsection (3), specify whether the drug or medicinal preparation and another drug or medicinal preparation should be treated as interchangeable on an individual patient basis" (section 101(3BA) of the Act).

- 6.18 The PBAC recalled that it has previously considered FP and ciclesonide to be non-inferior, and FP was accepted as being of acceptable cost-effectiveness for very

severe asthmatics (those covered by the previous authority listing) and equivalent to beclomethasone/budesonide in other asthmatics patients (Therapeutic Relativity Sheets, June 2015). The PBAC also recalled that it had previously considered FF to be non-inferior to FP in terms of safety and efficacy.

- 6.19 The PBAC also noted that as the change to the drug names relating to FF and FP would also require new drugs to be declared for the ICS/LABA combinations, fluticasone furoate with vilanterol, and fluticasone propionate with salmeterol, the committee is similarly required, under section under section 101(3BA) of the Act to specify whether the drug or medicinal preparation and another drug or medicinal preparation should be treated as interchangeable on an individual patient basis. The PBAC recalled that they previously advised, at the March 2014 meeting, that fluticasone with vilanterol should be treated as interchangeable on an individual patient basis with the combination drugs fluticasone with salmeterol; budesonide with eformoterol; and fluticasone with eformoterol; when these drugs are used to treat asthma.

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

7 PBAC Outcome

- 7.1 The PBAC recommended that fluticasone furoate and fluticasone propionate should be declared as different drugs for the purposes of section 85(2) of the *National Health Act 1953 (the Act)*. The PBAC therefore recommended the listing of fluticasone furoate, 100 mcg and 200 mcg powder for inhalation, as an unrestricted benefit for the treatment of asthma on a cost-minimisation basis to fluticasone propionate. The PBAC recalled its previous advice that the equi-effective doses are fluticasone furoate 100 microgram once daily and fluticasone propionate 250 microgram twice daily; and fluticasone furoate 200 microgram once daily and fluticasone propionate 500 microgram twice daily.
- 7.2 The PBAC also recommended that the current PBS listings for fluticasone (in the forms fluticasone propionate and fluticasone furoate) should be amended accordingly, with the listings under the current drug name revoked, and new drugs declared under section 85(2) of the Act, as summarised in the table below:

Brand name	Current drug name on the PBS to be revoked	Recommended drug name to be declared
Flixotide® (including Accuhaler and Junior Accuhaler)	fluticasone	fluticasone propionate
Breo® Ellipta®	fluticasone with vilanterol	fluticasone furoate with vilanterol
Seretide® (including Accuhaler and MDI)	fluticasone with salmeterol	fluticasone propionate with salmeterol

- 7.3 The PBAC advised, under Section 101(4AAB) of the Act, that it saw no reason why the Minister should not revoke the declarations that, fluticasone, fluticasone with vilanterol, and fluticasone with salmeterol are drugs to which Part VII of the Act applies. In providing this advice the PBAC noted that the Minister would only revoke those declarations at the same time as declaring fluticasone propionate, fluticasone furoate with vilanterol and fluticasone propionate with salmeterol to be drugs for the purposes of Part VII of the Act, with each of the new drugs being direct replacements for each delisted drug, respectively.
- 7.4 The PBAC noted the evidence presented in the submission suggested that the furoate and propionate esters of fluticasone led to differences in the pharmacokinetic and pharmacodynamic properties of fluticasone, similar to the magnitude of differences observed between different inhaled corticosteroids currently classed as separate drugs. The PBAC therefore considered that fluticasone furoate and fluticasone propionate be declared as different drugs.
- 7.5 The PBAC recommended under Section 101(3BA) of the Act that fluticasone furoate, fluticasone propionate, and ciclesonide should be treated as interchangeable on an individual patient basis.
- 7.6 The PBAC also recommended under Section 101(3BA) of the Act that the combination drugs fluticasone furoate with vilanterol, fluticasone propionate with salmeterol, budesonide with eformoterol, and fluticasone with eformoterol should be treated as interchangeable on an individual patient basis when these drugs are used to treat asthma.
- 7.7 The PBAC noted that this submission is not eligible for an Independent Review because it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Amend recommended listings as follows:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
FLUTICASONE <i>FUROATE</i>			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		

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Level / Method:	Unrestricted

8.2 Amend existing listings as follows:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
FLUTICASONE <i>PROPIONATE</i>				GSK
fluticasone propionate 100 microgram/actuation powder for inhalation, 60 actuations	1	5	Flixotide Junior Accuhaler	
fluticasone propionate 250 microgram/actuation powder for inhalation, 60 actuations	1	5	Flixotide Accuhaler	
fluticasone propionate 500 microgram/actuation powder for inhalation, 60 actuations	1	1	Flixotide Accuhaler	
fluticasone propionate 125 microgram/actuation pressurised inhalation, 120 actuations	1	5	Flixotide	
fluticasone propionate 250 microgram/actuation pressurised inhalation, 120 actuations	1	1	Flixotide	
fluticasone propionate 50 microgram/actuation pressurised inhalation, 120 actuations	1	5	Flixotide Junior	

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Level / Method:	Unrestricted

Public Summary Document – March 2017 PBAC Meeting

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
FLUTICASONE <i>PROPIONATE</i> + SALMETEROL			GSK
fluticasone propionate 100 microgram/actuation + salmeterol 50 microgram/actuation powder for inhalation, 60 actuations	1	5	Seretide Accuhaler 100/50
fluticasone propionate 250 microgram/actuation + salmeterol 50 microgram/actuation powder for inhalation, 60 actuations	1	5	Seretide Accuhaler 250/50
fluticasone propionate 500 microgram/actuation + salmeterol 50 microgram/actuation powder for inhalation, 60 actuations	1	5	Seretide Accuhaler 500/50
fluticasone propionate 50 microgram/actuation + salmeterol 25 microgram/actuation pressurised inhalation, 120 actuations	1	5	Seretide MDI 50/25
fluticasone propionate 125 microgram/actuation + salmeterol 25 microgram/actuation pressurised inhalation, 120 actuations	1	5	Seretide MDI 125/25
fluticasone propionate 250 microgram/actuation + salmeterol 25 microgram/actuation pressurised inhalation, 120 actuations	1	5	Seretide MDI 250/25

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Asthma
PBS Indication:	Asthma
Restriction Level / Method:	<input checked="" 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
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 4 years or over.

Public Summary Document – March 2017 PBAC Meeting

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
FLUTICASONE <i>PROPIONATE</i> + SALMETEROL fluticasone propionate 500 microgram/actuation + salmeterol 50 microgram/actuation powder for inhalation, 60 actuations	1	5	GSK Seretide Accuhaler 500/50
fluticasone propionate 250 microgram/actuation + salmeterol 25 microgram/actuation pressurised inhalation, 120 actuations	1	5	Seretide MDI 250/25

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Chronic Obstructive Pulmonary Disease (COPD)
PBS Indication:	Chronic Obstructive Pulmonary Disease (COPD)
Restriction Level / Method:	<input checked="" 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
Clinical criteria:	Patient must have a forced expiratory volume in 1 second (FEV1) less than 50% of predicted normal prior to therapy, AND Patient must have a history of repeated exacerbations with significant symptoms despite regular beta-2 agonist bronchodilator therapy, AND The treatment must be for symptomatic treatment.
Administrative Advice	Patient must not be on a concomitant single agent long-acting beta-2 agonist. This product is not indicated for the initiation of bronchodilator therapy in COPD.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
FLUTICASONE <i>FUROATE</i> + VILANTEROL fluticasone furoate 200 microgram/actuation + vilanterol 25 microgram/actuation powder for inhalation, 30 actuations	1	5	GSK Breo Ellipta 200/25

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Asthma
PBS Indication:	Asthma

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Restriction Level / Method:	<input checked="" 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
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.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
FLUTICASONE FUROATE + VILANTEROL fluticasone furoate 100 microgram/actuation + vilanterol 25 microgram/actuation powder for inhalation, 30 actuations	1	5	Breo Ellipta 100/25 GSK

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Asthma
PBS Indication:	Asthma
Restriction Level / Method:	<input checked="" 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
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:	This drug is not recommended nor PBS-subsidised for use as 'maintenance and reliever' therapy

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Chronic obstructive pulmonary disease (COPD)
PBS Indication:	Chronic obstructive pulmonary disease (COPD)
Restriction Level / Method:	<input checked="" 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

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

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

GSK welcomes the decision by the PBAC to recognise fluticasone furoate (FF) and fluticasone propionate (FP) as separate and distinct 'drugs' under section 85(2) of the Act.

Recognition of FF and FP as distinct 'drugs' is consistent with prior TGA and EMA evaluation of the respective new chemical entity applications. It is further consistent with the intended purpose of the 2007 NHA legislative amendment (as provided in the Explanatory Statement) to adopt a definition of 'drug', for the purpose of section 85(2) of the Act, as the 'active moiety'.