

Agenda item 12.01

Age restrictions on inhaled corticosteroid (ICS) + long-acting beta₂ agonist (LABA) fixed dose combination (FDC) products Correspondence from Clinician

1 Purpose of Item

- 1.1 To seek the PBAC's advice on the appropriateness of the current PBS age restrictions specified for inhaled corticosteroid (ICS) + long-acting beta₂ agonist (LABA) fixed dose combination (FDC) products.
- 1.2 The request for advice follows correspondence received on 1 April 2019 from a clinician regarding the appropriateness of prescribing ICS+LABA FDC products outside the current age restriction (i.e. to children under 12 years) for paediatric patients with fluticasone propionate + salmeterol failure.

2 Background

- 2.1 All ICS+LABA FDC products PBS listed for asthma have an age restriction specified in the restriction (Table 1). The age restrictions specified are consistent with either the TGA registered indication or recommended age in the TGA approved Product Information.

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Table 1: ICS+LABA FDC products PBS listed for asthma

Drug	Trade name	Dose form ^a , strength	Age restriction in PBS listing
Budesonide + formoterol	Symbicort	DPI budesonide 100 mcg + formoterol 6 mcg/dose MDI budesonide 50 mcg + formoterol 3 mcg/dose MDI budesonide 100 mcg + formoterol 3 mcg/dose MDI budesonide 200 mcg + formoterol 6 mcg/dose	≥ 12 yrs
	DuoResp, Symbicort	DPI budesonide 200 mcg + formoterol 6 mcg/dose DPI budesonide 400 mcg + formoterol 12 mcg/dose	≥ 12 yrs Symbicort 200/6 otherwise ≥ 18 yrs
Fluticasone propionate + formoterol	Flutiform	MDI fluticasone propionate 50 mcg + formoterol 5 mcg/dose MDI fluticasone propionate 125 mcg + formoterol 5 mcg/dose MDI fluticasone propionate 250 mcg + formoterol 10 mcg/dose	≥ 12 yrs
Fluticasone propionate + salmeterol	Seretide	DPI fluticasone propionate 100 mcg + salmeterol 50 mcg/dose DPI fluticasone propionate 250 mcg + salmeterol 50 mcg/dose DPI fluticasone propionate 500 mcg + salmeterol 50 mcg/dose MDI fluticasone propionate 50 mcg + salmeterol 25 mcg/dose	≥ 4 yrs
	Multiple ^b	MDI fluticasone propionate 125 mcg + salmeterol 25 mcg/dose MDI fluticasone propionate 250 mcg + salmeterol 25 mcg/dose	≥ 4 yrs
Fluticasone furoate + vilanterol	Breo	DPI fluticasone furoate 100 mcg + vilanterol 25 mcg/dose DPI fluticasone furoate 200 mcg + vilanterol 25 mcg/dose	≥ 12 yrs

^a Metered dose inhaler (MDI) and dry powder inhaler (DPI) preparations can be administered via different devices

^b Fluticasone + salmeterol Cipla inhaler, Pavitide, Salplus F Inhaler, Seretide

Source: p2, Table 1, Age restrictions on ICS+LABA FDC products PSD, July 2019

2.2 At the July 2019 PBAC meeting, the Drug Utilisation Sub Committee (DUSC) Secretariat provided data on the proportion of children who were using ICS+LABA FDC products outside of age recommendations in the Product Information (PI). The data presented is reproduced in Table 2.

Table 2: Dispensing of FDCs by age and proportion inconsistent with age recommendations

Medicine	Strength, Number of children* in 2018 (N), Number of dispensings in 2018 (D)	Product Information age recommendation Number of children outside the age recommendation in 2018 (n) (% of all children, n/N), Number of dispensings in 2018 (d), (% of all dispensings, d/D)
Fluticasone + Salmeterol	50/25mcg; 100/50mcg; N= 17,960 children; D= 41,192 dispensings;	Recommended age >=4 years, Outside recommendation: n=1084 (6.0%) d= 2021 (4.9%)
Fluticasone + Salmeterol	125/25mcg; 250/25mcg N= 29,118 children; D= 69,241 dispensings;	Recommended age >=12 years, Outside recommendation: n=10,527 (36.2%) d= 24,294 (35.1%)
Fluticasone + Salmeterol	250/50mcg; 500/50mcg; N= 2,954 children; D= 7,732 dispensings;	Recommended age >=12 years, Outside recommendation: n=439 (14.9%) d= 1,117 (14.5%)
Fluticasone + Salmeterol	Distinct children: 48,225; Total dispensings: 118,165	Outside recommendation: Distinct children: 11,978 (24.8% of all distinct children) Total dispensings: 27,432 (23.2% of total dispensings)
Budesonide + Formoterol	50/3mcg; 100/3mcg; 100/6mcg; 200/6mcg; N= 17,527 children; D= 33,200 dispensings;	Recommended age >=12 years, Outside recommendation: n= 4,208 (24.0%) d= 7,604 (22.9%)
Budesonide + Formoterol	400/12mcg N= 639 children; D= 1,513 dispensings;	Recommended age >=18 years, Outside recommendation: n= 639 (100%) d= 1,513 (100%)
Budesonide + Formoterol	Distinct children: 18,011; Total dispensings: 34,713	Outside recommendation: Distinct children: 4,836 (26.9% of all distinct children) Total dispensings: 9,117 (26.3% of total dispensings)
Fluticasone + Formoterol	50/5mcg; 125/5mcg; 250/10mcg; N= 1,838 children; D= 4,152 dispensings	Recommended age >=12 years Outside recommendation: n= 606 (33.0%) d= 1,235 (30.0%)
Fluticasone + Vilanterol	100/25mcg; 200/25mcg N= 3,350 children; D= 10,464 dispensings	Recommended age >=12 years, Outside recommendation: n= 362 (10.8% of all children) d= 1,027 (9.8% of all dispensings)
ALL FDC products	Distinct children: 69,844; Total dispensings: 167,494	Outside recommendations: Distinct children: 17,561 (25.1% of all distinct children) Total dispensings: 38,811 (23.2% of total dispensings)

* Children defined as those aged < 18 years

Source: p5, Table 2, Age restrictions on ICS+LABA FDC products PSD, July 2019

- 2.3 Fluticasone propionate + salmeterol is currently the only PBS listed ICS+LABA FDC product that is subsidised for use in patients aged 4–11 years. Use of this product was consistent with age restrictions in the PBS criteria in almost all cases.
- 2.4 24.0% (n=4,208) of children being treated with PBS subsidised budesonide + formoterol 50/3 mcg, 100/3 mcg, 100/6 mcg and 200/6 mcg products were aged <12 years. Use in this age group was inconsistent with the PBS criteria. It is unknown whether these children had previously failed treatment with fluticasone propionate + salmeterol.
- 2.5 At its July 2019 meeting, the PBAC noted the clinician’s correspondence and key concerns raised by a small number of paediatric respiratory specialists in relation to patients who have experienced fluticasone propionate + salmeterol failure. The PBAC

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noted that these included having to prescribe an alternative FDC therapy as a private script, or prescribers ignoring the authority age restriction thereby exposing themselves to audit (paragraph 3.1, Age restrictions on ICS+LABA FDC products Public Summary Document (PSD), July 2019).

- 2.6 The PBAC considered the following options in response to the concerns raised in the correspondence:
- Option 1: Retain current PBS age restrictions specified for ICS+LABA FDC products.
 - Option 2: Remove the minimum age limit for children specified in the PBS restrictions for all ICS+LABA FDC products.
 - Option 3: In addition to the existing PBS restrictions for ICS+LABA FDC products, create a separate Authority Required (STREAMLINED) code for ICS+LABA FDC products other than fluticasone propionate + salmeterol that is silent on age and restricts use to those who have failed fluticasone propionate + salmeterol (paragraph 3.2, Age restrictions on ICS+LABA FDC products PSD, July 2019).
- 2.7 The PBAC noted the concern about the use of FDCs as initiation therapy highlighted in the Asthma in Children Review. The PBAC considered the current PBS age restrictions to be an important way forward following this review and that their removal (or being silent on age) may remove the guidance for general practitioners. The PBAC therefore advised that Option 2 was not feasible (paragraph 3.3, Age restrictions on ICS+LABA FDC products PSD, July 2019).
- 2.8 The PBAC noted Option 1, i.e. retaining the current PBS age restrictions specified for ICS+LABA FDC products, but considered there may be a clinical need for an alternative solution. The PBAC requested the Department write to the Thoracic Society of Australia and New Zealand (TSANZ) to outline the concerns in the original correspondence and request information on the extent of fluticasone propionate + salmeterol failure in children aged 4 to 12 years (paragraph 3.4, Age restrictions on ICS+LABA FDC products PSD, July 2019).
- 2.9 In contacting TSANZ, the PBAC considered that the Secretariat would also need to indicate that the Committee is of a mind to keep the current restrictions, but with the addition of a new restriction for patients who require alternative therapies after fluticasone propionate + salmeterol failure (see Option 3). The PBAC considered that prescribing for this second-line listing would be limited to respiratory specialists. The PBAC acknowledged that such use would be outside of the TGA indication for ICS+LABA FDC products other than fluticasone propionate + salmeterol. Despite this, the PBAC considered that there was some evidence for use of alternative ICS+LABA FDC products in patients <12 years of age (e.g. budesonide + formoterol) (paragraph 3.5, Age restrictions on ICS+LABA FDC products PSD, July 2019).
- 2.10 In order to gain a better understanding of the extent of the issue, the PBAC also requested that the DUSC Secretariat provide information on initiation and sequencing data for the number of patients <12 years of age who have failed fluticasone

propionate + salmeterol before being prescribed budesonide + formoterol (paragraph 3.6, Age restrictions on ICS+LABA FDC products PSD, July 2019).

3 Current situation

- 3.1 TSANZ provided input on 20 November 2019, which outlined the following:
- Support for alternative agents to fluticasone propionate + salmeterol, such as budesonide + formoterol MDI, being made available to children ≥ 6 years to better align with the new Global Initiative for Asthma (GINA) guidelines.
 - Concern that some patients on fluticasone propionate + salmeterol fail to respond to treatment and, in a majority of patients, this is described as persistence of asthma symptoms or lack of asthma control despite therapy.
 - Support for prescribing by respiratory specialists in the paediatric population, noting that it would be important to also consider this for other FDC products on the PBS.
- 3.2 The DUSC Secretariat provided drug initiation sequence data for the 24.0% (n=4,208) of children being treated with PBS subsidised budesonide + formoterol 50/3 mcg, 100/3 mcg, 100/6 mcg and 200/6 mcg products and were aged <12 years of age (Table 3). Sequences are from 1 April 2012, the start of collection of under copayment prescriptions, to the end of December 2018. The most common treatment sequences were initiation with budesonide + formoterol (46.9%) or initiation with fluticasone before moving to budesonide + formoterol (25.4%). The initiation sequence included fluticasone + salmeterol before budesonide + formoterol in 18.9% (n=798) of the 4,208 children.

Table 3: Drug initiation sequence for children < 12 years or age prescribed PBS subsidised budesonide + formoterol 50/3mcg, 100/3mcg, 100/6mcg and 200/6mcg from 1 April 2012 to 31 December 2018

Drug (strength) initiation sequence	Patients	% Patients
budesonide + formoterol (4)	1,975	46.9
fluticasone -> budesonide + formoterol (4)	1,070	25.4
fluticasone + salmeterol (1) -> budesonide + formoterol (4)	275	6.5
fluticasone -> fluticasone + salmeterol (1) -> budesonide + formoterol (4)	152	3.6
fluticasone + salmeterol (2) -> budesonide + formoterol (4)	108	2.6
budesonide + formoterol (4) -> fluticasone	95	2.3
fluticasone + salmeterol (1) -> fluticasone + salmeterol (2) -> budesonide + formoterol (4)	87	2.1
fluticasone -> fluticasone + salmeterol (2) -> budesonide + formoterol (4)	81	1.9
fluticasone -> fluticasone + salmeterol (1) -> fluticasone + salmeterol (2) -> budesonide + formoterol (4)	59	1.4
budesonide -> budesonide + formoterol (4)	27	0.6
fluticasone + salmeterol (2) -> fluticasone + salmeterol (1) -> budesonide + formoterol (4)	23	0.5
budesonide + formoterol (4) -> fluticasone + salmeterol (2)	17	0.4
fluticasone -> budesonide -> budesonide + formoterol (4)	16	0.4
fluticasone -> fluticasone + salmeterol (2) -> fluticasone + salmeterol (1) -> budesonide + formoterol (4)	13	0.3
fluticasone -> budesonide + formoterol (4) -> fluticasone + salmeterol (2)	12	0.3
fluticasone -> budesonide + formoterol (4) -> fluticasone + salmeterol (1)	11	0.3
budesonide + formoterol (4) -> fluticasone + salmeterol (1)	10	0.2
fluticasone -> fluticasone + formoterol (6) -> budesonide + formoterol (4)	8	0.2
budesonide -> fluticasone -> budesonide + formoterol (4)	8	0.2
fluticasone + formoterol (6) -> budesonide + formoterol (4)	8	0.2
other sequences where patients <= 5	153	3.6
Total	4,208	100

fluticasone + salmeterol (1) = 50/25mcg,100/50mcg (items 8430q,8517g), fluticasone + salmeterol (2) = 125/25mcg,250/25mcg (items 8518h,8519j), fluticasone + salmeterol (3) = 250/50mcg, 500/50mcg (items 8431r,8432t), budesonide + formoterol (4) = 50/3mcg,100/3mcg, 100/6mcg, 200/6mcg (items 8625y, 8796y, 10015d, 10018g, 10024n, 11273h, 2867x, 2938p), budesonide + formoterol (5) = 400/12mcg (items 8750m,11301t), fluticasone + formoterol (6) = 50/5mcg,125/5mcg, 250/10mcg (items 2827t,10007q,10008r), fluticasone + vilanterol (7) = 100/25mcg, 200/25mcg (items 10167d, 10199t, 11124l, 11129r)

Source: D1161 – drug initiation sequence up to end of 2018 for 4,208 children – suppression of cells le 5

4 PBAC Outcome

- 4.1 In order to maintain a level of guidance for clinicians around the appropriate use of FDCs in children, the PBAC recommended that the existing PBS restrictions for ICS+LABA FDC products should be retained. The PBAC noted that the existing restrictions align with the Therapeutic Goods Administration (TGA) indications and product information (PI) for these products.
- 4.2 The PBAC recalled the clinician concerns raised in July 2019 regarding paediatric patients who experience fluticasone propionate + salmeterol failure, and reiterated its advice that there was a clinical need in this group that was not covered by the existing PBS restrictions. The PBAC recalled that the Thoracic Society of Australia and New Zealand (TSANZ) provided support for a new restriction for children ≥6 years who have failed fluticasone propionate + salmeterol, particularly in light of the revised Global Initiative for Asthma (GINA) guidelines. The PBAC also recalled the initiation and sequencing data provided by the Drug Utilisation Sub-Committee (DUSC) Secretariat of the Department for the number of patients <12 years of age who have

failed fluticasone propionate + salmeterol before being prescribed budesonide + formoterol. The PBAC considered that, whilst only a small percentage of patients (18.9%) fell into this category, a new restriction for this group was the most appropriate option to ensure asthma control for these individuals.

- 4.3 Therefore, in order to address the clinical need for children under the age of 12 who have experienced fluticasone propionate + salmeterol failure, the PBAC recommended the addition of a new Authority Required (STREAMLINED) listing for budesonide + formoterol FDC products (excluding budesonide + formoterol 400/12 mcg products) that is silent on age. This listing would restrict use to those who have failed fluticasone propionate + salmeterol, and prescribing would be limited to respiratory specialists and paediatricians. The PBAC noted there was published clinical data on use of budesonide + formoterol in patients aged <12 years of age and that the US Food and Drug Administration had approved budesonide + formoterol for use in this population. The PBAC considered these new listings should not be extended to other ICS+LABA FDC products noting the lack of clinical data on use of these products in patients under the age of 12.
- 4.4 The PBAC considered it would be appropriate to preclude budesonide + formoterol 400/12 mcg products from these new listings given that the 400/12 mcg strength is unlikely to be used in children aged <12 years.

5 Recommended listing

5.1 Add new items:

budesonide 50 mcg + formoterol 3 mcg and budesonide 100 mcg + formoterol 3 mcg (Symbicort Rapihaler MDI):

Name, Restriction, Manner of administration and form	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Name and Manufacturer
BUDESONIDE WITH FORMOTEROL budesonide 50 microgram/actuation + formoterol (eformoterol) fumarate dihydrate 3 microgram/actuation inhalation, 120 actuations	2	2	5	Symbicort Rapihaler 50/3 [10024N] AstraZeneca Pty Ltd
BUDESONIDE WITH FORMOTEROL budesonide 100 microgram/actuation + formoterol (eformoterol) fumarate dihydrate 3 microgram/actuation inhalation, 120 actuations	2	2	5	Symbicort Rapihaler 100/3 [10015D] AstraZeneca Pty Ltd
Category / Program:	GENERAL – General Schedule (Code GE)			
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives			
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input checked="" type="checkbox"/> Streamlined			

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[9277]	Indication: Asthma
New [25923]	Clinical criteria:
New [25918]	<i>Patient must have failed PBS-subsidised fluticasone propionate and salmeterol as a fixed dose combination for this condition.</i>
New [25922]	Treatment Criteria:
New [25920]	<i>Must be treated by a respiratory physician;</i>
	OR
[10064]	<i>Must be treated by a paediatrician.</i>
[22301]	Administrative Advice: This product is not indicated for the initiation of treatment in asthma.
[10615]	Administrative Advice: This drug is not PBS-subsidised for the treatment of chronic obstructive pulmonary disease (COPD).
[22302]	Administrative Advice: The patient must not be on a concomitant single agent long-acting-beta-2-agonist (LABA).
[21822]	Administrative Advice: A LABA includes olodaterol, indacaterol, salmeterol, formoterol or vilanterol.
[21825]	Administrative Advice: Adherence to current treatment and device (inhaler) technique should be reviewed at each clinical visit and before "stepping up" a patient's medication regimen.

budesonide 200 mcg + formoterol 6 mcg (Symbicort Rapihaler MDI):

Name, Restriction, Manner of administration and form	Max. qty packs	Max. qty units	№.of Rpts	Proprietary Name and Manufacturer
BUDESONIDE WITH FORMOTEROL budesonide 200 microgram/actuation + formoterol (eformoterol) fumarate dihydrate 6 microgram/actuation inhalation, 120 actuations	2	2	5	Symbicort Rapihaler 200/6 [10018G] AstraZeneca Pty Ltd

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input checked="" type="checkbox"/> Streamlined
[9277]	Indication: Asthma
New [25925]	Clinical criteria:
New [25918]	<i>Patient must have failed PBS-subsidised fluticasone propionate and salmeterol as a fixed dose combination for this condition.</i>
New [25922]	Treatment Criteria:
New [25920]	<i>Must be treated by a respiratory physician;</i>
	OR

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[10064]	<i>Must be treated by a paediatrician.</i>
[9915]	Administrative Advice: Unlike Symbicort Turbuhaler 200/6, Symbicort Rapihaler 200/6 is not recommended nor PBS-subsidised for use as 'maintenance and reliever' therapy as the approved Product Information does not specify such use.
[22301]	Administrative Advice: This product is not indicated for the initiation of treatment in asthma.
[22302]	Administrative Advice: The patient must not be on a concomitant single agent long-acting-beta-2-agonist (LABA)
[21822]	Administrative Advice: A LABA includes olodaterol, indacaterol, salmeterol, formoterol or vilanterol.
[21825]	Administrative Advice: Adherence to current treatment and device (inhaler) technique should be reviewed at each clinical visit and before "stepping up" a patient's medication regimen.

budesonide 100 mcg + formoterol 6 mcg (Symbicort Turbuhaler DPI) and budesonide 200 mcg + formoterol 6 mcg (Symbicort Turbuhaler/DuoResp Spiromax DPIs):

Name, Restriction, Manner of administration and form	Max. qty packs	Max. qty units	№.of Rpts	Proprietary Name and Manufacturer
BUDESONIDE WITH FORMOTEROL budesonide 100 microgram/actuation + formoterol (eformoterol) fumarate dihydrate 6 microgram/actuation powder for inhalation, 120 actuations	1	1	5	Symbicort Turbuhaler 100/6 [8796Y] AstraZeneca Pty Ltd
BUDESONIDE WITH FORMOTEROL budesonide 200 microgram/actuation + formoterol (eformoterol) fumarate dihydrate 6 microgram/actuation powder for inhalation, 120 actuations	1	1	5	Symbicort Turbuhaler 200/6 [8625Y] AstraZeneca Pty Ltd
				DuoResp Spiromax 200/6 [11273H] Teva Pharma Australia Pty Limited

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input checked="" type="checkbox"/> Streamlined
[9277]	Indication: Asthma
New [25926]	Clinical criteria:
New [25918]	<i>Patient must have failed PBS-subsidised fluticasone propionate and salmeterol as a fixed dose combination for this condition.</i>
New [25922]	Treatment Criteria:
New [25920]	<i>Must be treated by a respiratory physician;</i>
	OR

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[10064]	<i>Must be treated by a paediatrician.</i>
[22301]	Administrative Advice: This product is not indicated for the initiation of treatment in asthma.
[10615]	Administrative Advice: This drug is not PBS-subsidised for the treatment of chronic obstructive pulmonary disease (COPD).
[22302]	Administrative Advice: The patient must not be on a concomitant single agent long-acting-beta-2-agonist (LABA).
[21822]	Administrative Advice: A LABA includes olodaterol, indacaterol, salmeterol, formoterol or vilanterol.
[21825]	Administrative Advice: Adherence to current treatment and device (inhaler) technique should be reviewed at each clinical visit and before "stepping up" a patient's medication regimen.

6 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.