

**7.09 BUDESONIDE with FORMOTEROL,  
Powder for oral inhalation in breath actuated device  
containing budesonide 200 micrograms with  
formoterol fumarate dihydrate 6 micrograms per dose,  
120 doses (SYMBICORT Turbuhaler® 200/6),  
Pressurised inhalation containing budesonide 100  
micrograms with formoterol fumarate dihydrate 3  
micrograms per dose, 120 doses (SYMBICORT  
Rapihaler® 100/3),  
AstraZeneca Pty Ltd**

**1 Purpose of Application**

- 1.1 The minor resubmission requested an Authority Required (STREAMLINED) listing for budesonide with formoterol fixed dose combination (Symbicort) for asthma to include use as an anti-inflammatory reliever therapy administered as needed for adolescent and adult patients with mild asthma. The resubmission applies to the Symbicort 200/6 Turbuhaler and the Symbicort 100/3 Rapihaler only. A major submission for Symbicort for the proposed indication was considered at the July 2019 PBAC meeting.
- 1.2 To address concerns raised by the PBAC at its July 2019 meeting, the resubmission provided the following:
- A separate proposed PBS listing with fewer repeats (reduced from five to one) for 'as-needed' treatment, in addition to the current Symbicort listing for maintenance treatment;
  - Additional information in support of the non-inferiority clinical claim;
  - An amended cost-minimisation analysis; and
  - A proposed risk sharing arrangement (RSA).

**2 Requested listing**

- 2.1 The resubmission requested a new listing, with the following changes to the restriction proposed in July 2019:
- A stipulation that the use of Symbicort for allergen or exercise-induced bronchoconstriction is not PBS-subsidised;

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- One repeat for the new listing. The current listing is for five repeats.
- A stipulation that only one prescription (one original dispensing of the maximum quantity, plus one repeat) is permitted in a 12-month period to align with the trial result that an average of 1.58 inhalers were required.

2.2 Bold text (and bold strikethrough text) indicate the changes to the current restrictions proposed by the sponsor.

2.3 Suggestions and additions proposed by the Secretariat to the requested listing are shaded in grey with additions in italics and deletions in strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty (packs)	No. of repeats	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
BUDESONIDE + FORMOTEROL (EFORMOTEROL)budesonide 200 microgram/actuation + formoterol (eformoterol) fumarate dihydrate 6 microgram/actuation powder for inhalation, 120 actuations	1	1	\$44.79	SYMBICORT Turbuhaler 200/6 AstraZeneca Pty Ltd

<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>PBS Indication:</b>	Mild asthma
<b>Restriction Level / Method:</b>	<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
<b>Clinical criteria:</b>	<p><del>Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids; OR</del></p> <p><b>Patient must have asthma and require an anti-inflammatory reliever therapy;</b> OR</p> <p>Patient must have experienced frequent asthma symptoms while receiving treatment with oral or inhaled corticosteroids and require single maintenance and reliever therapy; OR</p> <p>Patient must have experienced frequent asthma symptoms while receiving treatment with a combination of an inhaled corticosteroid and long acting beta-2 agonist and require single maintenance and reliever therapy.</p>
<b>Population criteria:</b>	Patient must be aged 12 years or over.
<b>Administrative Advice:</b>	<p><del>This product is not indicated for the initiation of treatment in asthma</del></p> <p>This drug is not PBS-subsidised for the treatment of <i>chronic obstructive pulmonary disease</i> (COPD) or for the treatment of allergen- or exercise-induced bronchoconstriction.</p> <p>The patient must not be on a concomitant single <i>agent</i> long-acting-beta-2-agonist (LABA)</p> <p>A LABA includes olodaterol, indacaterol, salmeterol, formoterol or vilanterol.</p> <p>Adherence to current treatment and device (inhaler) technique should be reviewed at each clinical visit and before 'stepping up' a patient's medication regimen.</p>

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	A single prescription (one original supply plus one repeat) is permitted in any 12-month period. If more frequent treatment is required, consider whether a maintenance treatment regimen would be more appropriate.
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Name, Restriction, Manner of administration and form	Max. Qty (packs)	No. of repeats	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
BUDESONIDE + FORMOTEROL (EFORMOTEROL) budesonide 100 microgram/actuation + formoterol (eformoterol) fumarate dihydrate 3 microgram/actuation powder for inhalation, 120 actuations	2	1	\$49.47	SYMBICORT Rapihaler 100/3 AstraZeneca Pty Ltd

<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>PBS Indication:</b>	Mild asthma
<b>Restriction Level / Method:</b>	<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
<b>Clinical criteria:</b>	<p><del>Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids; OR</del></p> <p><del>Patient must have asthma and require an anti-inflammatory reliever therapy; OR</del></p> <p><del>Patient must have experienced frequent asthma symptoms while receiving treatment with oral or inhaled corticosteroids and require single maintenance and reliever therapy; OR</del></p> <p><del>Patient must have experienced frequent asthma symptoms while receiving treatment with a combination of an inhaled corticosteroid and long-acting beta-2 agonist, and require single maintenance and reliever therapy.</del></p>
<b>Population criteria:</b>	Patient must be aged 12 years or over.
<b>Administrative Advice:</b>	<p><del>This product is not indicated for the initiation of treatment in asthma</del></p> <p>This drug is not PBS-subsidised for the treatment of <i>chronic obstructive pulmonary disease</i> (COPD) or for the treatment of allergen- or exercise-induced bronchoconstriction.</p> <p>The patient must not be on a concomitant single <i>agent</i> long-acting-beta-2-agonist (LABA)</p> <p>A LABA includes olodaterol, indacaterol, salmeterol, formoterol or vilanterol.</p> <p>Adherence to current treatment and device (inhaler) technique should be reviewed at each clinical visit and before 'stepping up' a patient's medication regimen.</p> <p><b>A single prescription (one original supply plus one repeat) is permitted in any 12-month period. If more frequent treatment is required, consider whether a maintenance treatment regimen would be more appropriate.</b></p>

For more detail on PBAC's view, see section 5 PBAC outcome.

### **3 Background**

#### ***Registration status***

- 3.1 The July 2019 major submission was made under TGA/PBAC Parallel Process. The PBAC noted that as of 18 July 2019 and 6 August 2019 the TGA registered indication for Symbicort 200/6 Turbuhaler and Symbicort 100/3 Rapihaler is: “for the treatment of asthma, to achieve overall asthma control, including the relief of symptoms and the reduction of the risk of exacerbations”. The TGA approved Product Information (PI) states that Symbicort can be used according to different treatment approaches:
- Anti-inflammatory reliever therapy (patients with mild disease);
  - Anti-inflammatory reliever plus maintenance therapy;
  - Maintenance therapy (fixed dose).

#### ***Previous PBAC consideration***

- 3.2 In July 2019, the PBAC did not recommend an extension of the current Authority Required (STREAMLINED) listing for Symbicort to include use as an anti-inflammatory reliever therapy administered as needed for adolescent and adult patients with mild asthma. The recommendation was primarily based on concerns regarding the claim of non-inferior clinical effectiveness compared with inhaled corticosteroid (ICS) + short-acting beta2-agonist (SABA), the approach taken in the cost-minimisation analysis, and that the financial consequences of listing were uncertain (paragraph 7.1, Symbicort, Public Summary Document (PSD), July 2019 PBAC meeting).
- 3.3 At its July meeting, the PBAC recommended that, before making a resubmission, the sponsor consult with asthma related organisations such as the National Asthma Council Australia (NAC), Asthma Australia and Lung Foundation Australia regarding how the proposed listing would likely work in clinical practice. The PBAC also advised that a resubmission would need to include a revised cost-minimisation analysis and financial estimates, noting that an RSA which includes a cap may be the most appropriate way forward in addressing the financial uncertainty (paragraph 7.14, Symbicort, PSD, July 2019 PBAC meeting).
- 3.4 The outstanding matters of concern from the July 2019 meeting and how they are addressed in the resubmission are summarised in the table below.

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**Table 1: PBAC matters of concern in previous consideration (July 2019)**

<b>Matters of concern</b>	<b>How the resubmission addresses it</b>
<p>The PBAC noted the consumer comments from three key asthma related organisations (NAC, Asthma Australia and The Lung Foundation). The PBAC was concerned that while they described benefits of treatment with Symbicort, the Asthma Australia comments raised concerns over how the requested listing would be implemented in practice (paragraph 7.2, Symbicort, PSD, July 2019 PBAC meeting).</p>	<p>An amended (separate) PBS listing with fewer repeats (reduced from five to one) to better align with the irregular pattern of 'as-needed' use and to signal to prescribers those patients who would be better served with a maintenance treatment regimen.</p> <p>The resubmission also stated that the sponsor is currently consulting key asthma organisations to address the implementation of the extended listing of Symbicort in clinical practice. The development of a formal statement was not possible at the time of the minor submission deadline.</p>
<p>The PBAC was concerned the SYGMA 1 trial reported that Symbicort had 36% lower odds of achieving a WCAW compared to ICS+SABA in SYGMA 1 (OR 0.64, 95% CI:0.57, 0.73). WCAW was the primary outcome from the SYGMA 1 trial.</p> <p>In addition, the PBAC was concerned regarding the submission's claim of non-inferiority compared to ICS+SABA for the primary outcome in the SYGMA 2 trial. No significant differences in the annual rate of severe asthma exacerbations was reported in SYGMA 2 between Symbicort and ICS+SABA arms (RR = 0.97, 1-sided upper 95% CI: 1.16). The PBAC noted that non-inferiority was declared when the upper 95% CI of the severe asthma exacerbation rate ratio (Symbicort vs ICS+SABA) was &lt; 1.20. The PBAC agreed with the ESC that, as per EMA guidelines for when trial objectives change from demonstrating superiority to non-inferiority, a 97.5% CI would be more appropriate.</p> <p>As such, the PBAC considered that the non-inferiority claim was not robust as the upper limit of the 97.5% CI was 1.20 for the supportive efficacy analysis (paragraph 7.6, Symbicort, PSD, July 2019 PBAC meeting).</p>	<p>Additional information to clarify the clinical data submitted in support of the non-inferiority claim with respect to WCAW and use of 97.5% CIs to evaluate the rate of severe asthma exacerbations.</p>
<p>The PBAC considered that the cost-minimisation analysis versus ICS+SABA was the most appropriate economic analysis for this submission. The PBAC noted that using AEMP, applying the correct therapeutic equivalent dose of salbutamol and excluding the use of private prices, the cost per patient per year for Symbicort was \$6.79 more than ICS+SABA in mild asthma. In addition, the PBAC agreed with the ESC that patients who use as needed asthma therapy are likely to have more than one Symbicort inhaler in use at a time as is often the case with SABAs, which would affect the results of the cost-minimisation analysis. As such, the PBAC considered that the cost-minimisation analysis presented did not support the claim that, at the price requested, the cost of Symbicort to the health system is, at most, equivalent to ICS+SABA (paragraph 7.10, Symbicort, PSD, July 2019 PBAC meeting).</p>	<p>An amended cost-minimisation analysis. Market split no longer assumed to be 93% and 7% for the Turbuhaler and Rapihaler respectively. Adjusted to 60% and 40%. Dose for salbutamol also adjusted.</p>
<p>The PBAC agreed with DUSC that the certainty around the financial estimates was low, with use likely to be high and beyond the proposed estimates. The PBAC disagreed with the pre-PBAC response that the average number of packs per patient per year proposed in the submission (1.58) was appropriate. The PBAC noted the proposed Symbicort PI states that patients should be advised to always have</p>	<p>An RSA proposed.</p>

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Matters of concern	How the resubmission addresses it
Symbicort available for relief of symptoms and that a separate short-acting bronchodilator for relief of symptoms is not required. As such, the PBAC agreed with the DUSC that patients are likely to have more than one Symbicort inhaler in use at a time and considered that this would affect the financial estimates. The PBAC also considered there was potential for an increased number of patients to commence treatment with Symbicort, instead of a low dose ICS. The PBAC considered that an RSA may be required for Symbicort to address the risk of use beyond the proposed population and to address the uncertain financial estimates (paragraph 7.12, Symbicort, PSD, July 2019 PBAC meeting).	

CI = confidence intervals, RSA = Risk sharing arrangement, WCAW = Well Controlled Asthma Week  
 Source: Symbicort, PSD, July 2019 PBAC meeting, Current minor resubmission. Compiled by the Secretariat.

*For more detail on PBAC’s view, see section 5 PBAC outcome.*

## 4 Consideration of the evidence

### **Sponsor hearing**

4.1 There was no hearing for this item as it was a minor submission.

### **Consumer comments**

4.2 In July 2019, the PBAC noted and welcomed the input from individuals (1), health care professions (3) and organisations (3). Some of the consumer comments described the benefits of treatment with Symbicort, including less reliance on short-acting reliever therapy and better control of asthma symptoms. However, in July 2019 the PBAC also noted that Asthma Australia raised concerns regarding how the requested listing would be implemented in practice – particularly whether Symbicort would be used first line in place of SABA and concerns around ‘as needed’ use and the potential for increased ICS exposure in adolescents (paragraph 6.2, Symbicort, PSD, July 2019 PBAC meeting).

4.3 For the current resubmission, the PBAC noted and welcomed the input from individuals (1), health care professionals (1) and organisations (3). The PBAC also noted that all three asthma related organisations providing comments (NAC, Asthma Australia and The Lung Foundation) were supportive of the listing. Asthma Australia and health care professional input acknowledged the evidence from the SYGMA 1, SYGMA 2, Novel START<sup>1</sup> and PRACTICAL<sup>2</sup> trials underpinning the Symbicort mild

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<sup>1</sup> Beasley R, et al. Controlled Trial of Budesonide-Formoterol as Needed for Mild Asthma. N Engl J Med 2019;380:2020-30

<sup>2</sup> Hardy J, et al. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. Lancet 2019; 394: 919–28

asthma protocol, although Asthma Australia suggested the weight of evidence supports use in people > 18 years. Asthma Australia also highlighted the need for proper education of prescribers, dispensers and consumers including updated asthma management plans to assist implementation in practice. The pre-PBAC response agreed with Asthma Australia regarding the importance of education activities and outlined proposed quality use of medicines initiatives to support the use of Symbicort. The pre-PBAC response also stated that the safety and efficacy of Symbicort in adolescent patients (aged 12 to 17 years) has been established in the course of the TGA registration process for both the existing maintenance therapy indication and for anti-inflammatory reliever therapy.

### ***Clinical claim***

- 4.4 The July 2019 major submission claimed that Symbicort used as an anti-inflammatory reliever, as needed, in patients with mild asthma is equivalent (i.e. non-inferior) to ICS+SABA in terms of comparative effectiveness and comparative safety (paragraph 6.35, Symbicort, PSD, July 2019 PBAC meeting). At that time, while the PBAC considered the claim of comparable safety versus ICS+SABA as needed to be reasonable, they considered that the claim of non-inferior comparative effectiveness versus ICS+SABA was uncertain, due to concerns with the results reported for severe asthma exacerbations and Well Controlled Asthma Weeks (WCAW) (paragraphs 7.7 and 7.8, Symbicort, PSD, July 2019 PBAC meeting).

#### Well-Controlled Asthma Weeks (WCAW)

- 4.5 The resubmission stated that the WCAW measure inherently biases against Symbicort when comparing to ICS+SABA and hence the results of this symptom control endpoint must be interpreted with caution. The resubmission noted that, by definition, under the treatment regimen 'as needed' Symbicort is not taken unless a patient experiences symptoms. The resubmission argued that amongst the WCAW components, the largest difference between Symbicort and ICS+SABA arms was seen for the as-needed medication use component, in favour of ICS+SABA. Hence, the treatment comparison between Symbicort and ICS+SABA on the WCAW is more of a reflection of the different treatment regimens. At its July 2019 meeting the PBAC noted that a pre-planned additional analysis that removed the 'as needed' component from the WCAW composite measure still favoured ICS+SABA over Symbicort. At that time, the PBAC noted that only a post-hoc analysis where the first two inhalations used 'as needed' per day were not counted (i.e. the inhalations were included as if they had been taken as maintenance doses) showed comparable results between Symbicort and ICS+SABA (paragraph 6.23, Symbicort, PSD, July 2019 PBAC meeting).
- 4.6 The PBAC recalled that in the SYGMA 1 trial, Symbicort had 36% lower odds of achieving a WCAW compared with ICS+SABA during the study period (34.4% vs. 44.4%, Odds Ratio (OR) 0.64, 95 CI: 0.57,0.73)(paragraph 6.23, Symbicort, PSD, July 2019 PBAC meeting). The PBAC noted that removing the 'as needed' component from the

WCAW composite measure resulted in Symbicort having a 22% lower odds of achieving a WCAW compared to ICS+SABA during the study period (46.6% vs 52.9%. OR 0.78, 95 CI: 0.69, 0.88)<sup>3</sup>.

- 4.7 The resubmission stated that the July 2019 submission had nominated symptom control based on the Asthma Control Questionnaire-5 (ACQ-5) as the most relevant outcome, as it is the most widely used composite measure of asthma symptom control with a well-established and validated minimally clinically important difference (MCID) threshold. ACQ-5 was a secondary end-point in both the SYGMA 1 and SYGMA 2 trials. At its July 2019 meeting the PBAC noted the trials showed that both treatments improved ACQ-5 from baseline; however none of the improvement in ACQ-5 exceeded the MCID threshold of -0.5 points in any of the treatment arms (paragraph 6.22, Symbicort, PSD, July 2019 PBAC meeting).

#### Use of 97.5% CIs to evaluate asthma exacerbation reduction rate

- 4.8 The resubmission noted that the July 2019 evaluation for Symbicort posited that because ‘a protocol amendment was made to change the trial objective from demonstrating superiority to non-inferiority. In such instances European Medicines Agency (EMA) guidelines recommend that if one-sided confidence intervals (CI) are used they should be used with a coverage probability of 97.5%.<sup>4</sup> The submission used a coverage probability of 95%’ (paragraph 6.16, Symbicort, PSD, July 2019 PBAC meeting). The resubmission argued that the approach taken by the EMA has not been the practice in Australia and hence it would be reasonable for the non-inferiority of Symbicort to ICS+SABA to be considered using 95% CI. The sponsor stated the following reasons:

- The TGA and the PBAC guidelines both specify 95% CI and make no reference to 97.5% one-sided CIs.
- The PBAC has recommended submissions based on non-inferiority trials with 95% CIs (e.g. alirocumab in March 2019; inotuzumab ozogamicin in November 2018).
- The sponsor was unable to locate previous examples of PBAC cost-minimisation recommendations with a 97.5% CI.

#### Novel START and PRACTICAL trials

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<sup>3</sup> Table 28, pg96, SYGMA 1 Clinical Study Report. A 52-week, double-blind, randomised, multi-centre, parallel-group, Phase III study in patients 12 years and older with asthma, evaluating the efficacy and safety of Symbicort (budesonide/formoterol) Turbuhaler 160/4.5 mg ‘as needed’ and with Pulmicort (budesonide) Turbuhaler 200 microgram twice daily plus SABA Turbuhaler 0.4 mg as needed. February 2018.

<sup>4</sup> EMA guidance, Points to consider on switching between superiority and non-inferiority, July 2000. Available at [https://www.ema.europa.eu/en/documents/scientific-guideline/points-consider-switching-between-superiority-non-inferiority\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/points-consider-switching-between-superiority-non-inferiority_en.pdf)

- 4.9 The PBAC recalled that, in addition to the SYGMA 1 and SYGMA 2 trials, the July 2019 submission had identified two other relevant randomised, open-label trials (i) Novel START and (ii) PRACTICAL with the results not available at the time of submission or evaluation. As per paragraph 4.3, the PBAC noted that the results of both of these trials were now available.<sup>5,6</sup>
- 4.10 In Novel START (n=668), adults with mild asthma on SABA alone were randomised to either: SABA (salbutamol) as needed; budesonide twice daily plus SABA as needed (ICS+SABA group); or Symbicort as needed.<sup>4</sup> The primary outcome was annualised rate of asthma exacerbations.<sup>4</sup> The PBAC noted the rate of asthma exacerbations in the Symbicort group was lower than that in the SABA group (relative rate, 0.49; 95% CI: 0.33, 0.72) but did not differ significantly from that in the ICS+SABA group (relative rate, 1.12; 95% CI: 0.70, 1.79).<sup>4</sup> The PBAC also noted that the number of severe exacerbations in the Symbicort arm was lower than the number in both the SABA (9 vs 23; relative risk, 0.40; 95% CI: 0.18, 0.86) and the ICS+SABA group (9 vs 21; relative risk, 0.44; 95% CI: 0.20, 0.96).<sup>4</sup>
- 4.11 In the PRACTICAL trial (n=885), adults with mild to moderate asthma were randomised to either: budesonide twice daily plus terbutaline as needed (ICS+SABA group); or Symbicort as needed.<sup>5</sup> The PBAC noted the primary outcome was the rate of severe asthma exacerbations per patient per year, with the relative rate 0.69 (95% CI: 0.48, 1.00; p value = 0.049) for Symbicort as needed versus ICS+SABA.<sup>5</sup> The PBAC also noted the combined moderate and severe asthma exacerbation rate was lower with Symbicort than ICS+SABA (relative rate, 0.70; 95% CI: 0.51, 0.95) and that 60% less ICS was consumed in the Symbicort arm.<sup>5</sup>

### ***Economic analysis***

- 4.12 At its July 2019 meeting, the PBAC considered that a cost-minimisation base case that incorporated the likelihood of a patient having more than one Symbicort inhaler in use at a time and a more conservative split between the Symbicort Turbuhaler 200/6 and Symbicort Rapihaler 100/3 devices would be more appropriate (paragraph 7.10, Symbicort, PSD, July 2019 PBAC meeting).
- 4.13 The resubmission presented an updated cost-minimisation analysis (see Table 2), which included the following changes:

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<sup>5</sup> Beasley R, et al. Controlled Trial of Budesonide–Formoterol as Needed for Mild Asthma. *N Engl J Med* 2019;380:2020-30

<sup>6</sup> Hardy J, et al. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. *Lancet* 2019; 394: 919–28

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- The market split between the devices (Symbicort Turbuhaler 200/6 and Symbicort Rapihaler 100/3) was adjusted to 60% and 40% respectively (changed from the 93% and 7% assumption in the previous submission).
- The dose for salbutamol was adjusted based on ESC advice.

**Table 2: Updated cost-minimisation analysis (based on DPMQ)**

	Symbicort Turbuhaler 200/6 mcg	Symbicort Rapihaler 100/3 mcg	budesonide Turbuhaler 200 mcg (PBS item 2071B)	salbutamol 100 mcg (PBS item 8288F)
Equi-effective doses: budesonide or salbutamol (mean mcg per day) [A]	83.2		201	78.4
No. of Inhalations per pack [B]	120		200	200
Maximum Qty (packs) [C]	1	2	1	2
no of doses (based on max quantity dispensed) [D=BxC]	120		200	400
Delivered dose (mcg) [E]	160		160	100
DPMQ [F]	\$44.64	\$49.31	\$28.74	\$18.75
Price per delivered dose [G=F/D]	\$0.37	\$0.41	\$0.14	\$0.05
% of use [H]	60%	40%	100%	100%
Price per dose (Weighted price), \$ [I=G*H]	\$0.39		\$0.14	\$0.05
Cost per patient per day based on equi-effective doses [J=IxA/E]	\$0.20		\$0.18	\$0.04
Cost per patient per year [K=Jx365]	\$73.56		\$65.89	\$13.41
<b>Cost per patient/year by Comparator</b>				
SYMBICORT	\$73.56			
ICS+SABA	\$79.30			
Cost difference (Symbicort minus ICS+SABA)	-\$5.74			

DPMQ=dispensed price for maximum quantity

Source: Page 10 of the minor resubmission. PBS prices correct as at 01 June 2019.

- 4.14 As a minor submission, the cost-minimisation analysis has not been independently evaluated.
- 4.15 Unchanged from July 2019, the resubmission continued to argue that their approach using DPMQ for the cost-minimisation analysis was appropriate and consistent with other examples. Hence, the resubmission did not use AEMP in the updated cost-minimisation analysis presented. In July 2019, the ESC noted that pricing agreements are made by Government under the *National Health Act 1953* at the ex-manufacturer level and, as such, the prices would be agreed on this basis. It is not usually the case that pharmacy and wholesaler mark-ups are considered for the purpose of cost-minimisation as they do not relate to the cost of the medicine. At that time, the PBAC agreed with the ESC and supported the analysis based on ex-manufacturer prices

(paragraph 6.47, Symbicort, PSD, July 2019 PBAC meeting). In the revised cost-minimisation analysis, using the AEMP based on the requested DPMQ for Symbicort Turbuhaler 200/6 (\$30.98), Symbicort Rapihaler 100/3 (\$35.32), and the AEMP for the comparators, budesonide Turbuhaler 200mcg (\$16.19) and salbutamol 100mcg (\$3.90x2), the cost per patient per year for Symbicort would be \$9.05 more than ICS+SABA in mild asthma. The PBAC reiterated its July 2019 advice that a cost-minimisation analysis should be conducted based on ex-manufacturer prices (paragraph 6.47, Symbicort, PSD, July 2019 PBAC meeting).

- 4.16 Also unchanged from July 2019, the resubmission maintained it is unlikely that patients using Symbicort as needed will require multiple concurrent inhalers. Hence, the resubmission did not factor this into the revised cost-minimisation analysis. This approach is inconsistent with the PBAC's July 2019 recommendation that the cost-minimisation base case should incorporate the likelihood of a patient having more than one Symbicort inhaler in use at a time (see paragraph 4.12).

***Drug cost/patient/year: \$73.56***

- 4.17 In the July 2019 submission, applying the AEMP and excluding non-PBS prices for the comparators, the annual cost per patient was \$49.49 for Symbicort (\$6.79 more than ICS+SABA).
- 4.18 Based on a revised cost-minimisation analysis based on DPMQ, the resubmission estimated the annual cost per patient was \$73.56 for Symbicort (\$5.74 less than ICS+SABA).

***Estimated PBS usage & financial implications***

- 4.19 In the July 2019 submission DUSC considered the estimates presented to be underestimated. The main issues were:
- The requested change to the PBS restriction would allow Symbicort to be used as initiation therapy in asthma of any severity where use of an ICS is appropriate. This is consistent with the proposed TGA indication and the Global Initiative for Asthma (GINA)(2019) framework, which no longer recommend the use of SABA without an ICS. However, it was inconsistent with the population presented in the PICO, and the clinical trial evidence presented, which was patients uncontrolled on SABA or controlled on ICS+SABA.
  - The proportion of people who purchase SABA over-the-counter (OTC) only who would present to a GP for review with the availability of Symbicort as needed may depend on asthma counselling in pharmacies.
  - The uptake rates for patients uncontrolled on SABA were not justified. Despite the likely promotion of Symbicort as needed, the uptake is probably overestimated in

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year one, but would likely be higher than estimated by year six. Price is likely to be a factor for some patients, as Symbicort is more expensive than OTC SABA.

- Assumed MBS cost offsets for decreased GP visits may not be realised, as MBS costs for patients who were previously not seeing a GP for their asthma were not included.
- The number of packs dispensed is likely to be higher than predicted due to more frequent dosing than expected and some patients requiring additional inhalers to keep in different locations.
- The split between Symbicort Turbuhaler 200/6 and Symbicort Rapihaler 100/3 was assumed to be 93% and 7%, respectively. Patients who are familiar with a SABA aerosol puffer may prefer the Rapihaler as it is a more similar device (paragraph 6.62, Symbicort, PSD, July 2019 PBAC meeting).

4.20 The resubmission applied an adjusted market device split to the financial estimates, i.e. 60% and 40% for the Turbuhaler and Rapihaler respectively. The sponsor stated that this was the only amendment made to the utilisation and cost workbook from the July 2019 major submission. The July 2019 submission included estimated savings to the MBS based on the cost-utility analysis comparing Symbicort to SABA. These cost offsets were not included in the resubmission.

4.21 The resubmission estimated a net cost to the PBS/RPBS of less than \$10 million in Year 6 of listing, with a total net cost to the PBS of \$30 - 60 million over the first 6 years of listing. This is summarised in the table below as well as the expected patient and prescription numbers.

Table 3: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients treated						
Number of scripts dispensed <sup>a</sup>						
<b>Estimated financial implications of Symbicort<sup>b</sup></b>						
Cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Copayments	\$	\$	\$	\$	\$	\$
Cost to PBS/RPBS less copayments	\$	\$	\$	\$	\$	\$
<b>Estimated financial implications for ICS</b>						
Cost-offsets to PBS/RPBS	\$	\$	\$	\$	\$	\$
<b>Net financial implications<sup>b</sup></b>						
Net cost to PBS/RPBS	\$	\$	\$	\$	\$	\$

<sup>a</sup> Average number of units per year (1.58) based on the average dose (83.2mcg/day) in SYGMA 2 trial and inhalations per Symbicort pack  
<sup>b</sup> The split between the beneficiary types of RPBS services for Symbicort Rapihaler 100/3 (item code 10015D) and Turbuhaler 200/6 (item code 8625Y) was corrected during the development of the minor overview to 74.42% and 25.58% (J27 and K27 in Sheet 2b excel workbook)  
 Source: Page 4 of the minor resubmission, Attachment 3\_Utilisation-and-cost-model Workbook.

The redacted table shows that at Year 6, the estimated number of patients was 100,000 – 200,000.

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- 4.22 As a minor submission, the financial estimates have not been independently evaluated.
- 4.23 The PBAC noted that, as outlined in paragraph 4.19, the uptake rate and number of inhalers per year were key areas of concern raised by DUSC in July 2019. The PBAC recalled that the uptake rate used in Table 3 was 25% in Year 1, 28% in Year 2, 30% in Year 3 and 32% in Year 4 to Year 6. In addition, the PBAC noted that the average number of Symbicort scripts dispensed in Table 3 was based on an average of 1.58 units per patient per year.
- 4.24 The PBAC considered that, in addition to the market device split of 60% and 40% for the Turbuhaler and Rapihaler respectively, it would be appropriate to assume a revised uptake rate of 25% in Year 1, 28% in Year 2, 40% in Year 3 and 42% in Years 4 to 6 (i.e. increased by 10% for Years 3-6 only) and that 3.042 inhalers would be used per patient. The PBAC noted that applying these assumptions would result in a financial estimated net cost to the PBS/RPBS, based on the requested DPMQ, of \$10 - \$20 million in Year 6 of listing, with a total net cost to the PBS of \$60 - \$100 million over the first 6 years of listing (Table 4). However, the PBAC noted that the financial estimates would need to be recalculated to take into account the outcome of its considerations regarding the cost-minimisation analysis. The PBAC considered that on this basis, its previous concerns regarding the risk of use beyond the proposed estimates and resulting low certainty in the financial estimates were adequately addressed.

Table 4: Estimated use and financial implications (based on the requested DPMQ)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients treated <sup>a</sup>						
Number of scripts dispensed <sup>b</sup>						
<b>Estimated financial implications of Symbicort<sup>b</sup></b>						
Cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Copayments	\$	\$	\$	\$	\$	\$
Cost to PBS/RPBS less copayments	\$	\$	\$	\$	\$	\$
<b>Estimated financial implications for ICS</b>						
Cost-offsets to PBS/RPBS	\$	\$	\$	\$	\$	\$
<b>Net financial implications<sup>c</sup></b>						
Net cost to PBS/RPBS	\$	\$	\$	\$	\$	\$

<sup>a</sup> Noted that the resubmission incorrectly applied a RPBS split of 1.89% to both SABA uncontrolled population and ICS population rather than to the ICS population only. Impact on patient numbers is small. To be corrected when the financial estimates are recalculated as per paragraph 4.24.

<sup>b</sup> Average number of units per year was changed to 3.042 (F73 = 1.00, F74 = 2.00 in Sheet 3a. Volumes – new)

<sup>c</sup> The split between the beneficiary types of RPBS services for Symbicort Rapihaler 100/3 (item code 10015D) and Turbuhaler 200/6 (item code 8625Y) was corrected during the development of the minor overview to 74.42% and 25.58% (J27 and K27 in Sheet 2b excel workbook). The uptake rate was changed to 40% in Year 3 (E46 in Sheet 2a. Patients epi) and 42% in Years 4 to 6 (F46, G46, H46 in Sheet 2a. Patients epi).

Source: Attachment 3\_Utilisation-and-cost-model Workbook.

### **Financial Management – Risk Sharing Arrangements**

- 4.25 The minor resubmission proposed an RSA to address some of the uncertainty around the financial consequences of the proposed listing.
- 4.26 According to the resubmission, in July 2019, the PBAC identified two main drivers of the risk of over-utilisation:
- The number of potential additional patients; and
  - The number of scripts dispensed per patient.
- 4.27 The proposed RSA is based on the Symbicort utilisation estimates (number of patients treated, number of scripts dispensed) from the July 2019 submission (see Table 3 above). The financial estimates submitted in the July 2019 major submission assumed year 1 is 2019. These utilisation estimates will need to be adjusted based on year of implementation.
- 4.28 The minor resubmission proposed the following rebate arrangement to manage the risk of both additional patients and scripts:
- A [REDACTED] % rebate on each pack dispensed above the estimated script volumes up to [REDACTED] % of the estimates;
  - A [REDACTED] % rebate on each pack dispensed above [REDACTED] % of the estimates.
- 4.29 The sponsor claimed that the proposed rebate levels ensure that, even if the caps are exceeded, the PBS will pay no more for Symbicort than for an ICS+SABA that patients would otherwise receive.
- 4.30 The minor resubmission proposed the following additional elements in order to address issues relating to price disclosure and the presence of generic competition:
- In the event that a future Statutory Price Reduction (SPR) brings the un-rebated price of Symbicort to a level below the cost of ICS+SABA, it is proposed that the Deed be terminated;
  - In the event that a SPR price reduction brings any rebated price of Symbicort to a level below the cost of ICS+SABA, the rebate level would be altered to reflect the price equivalent to ICS+SABA;
  - It is proposed that the Deed be terminated if, for any reason, an RSA is deemed unnecessary in the context of generic competition for this indication.
  - It is proposed that any rebates paid to the Commonwealth for utilisation above the specified caps should be excluded from future price disclosure calculations.
- 4.31 The Secretariat noted that it is not consistent with policy and practice to implement rebate Deeds for multi-branded PBS medicines. The pre-PBAC response

acknowledged that an RSA arrangement for Symbicort is somewhat unusual given it is off-patent and in F2. The pre-PBAC response stated that while F2 drugs do not typically require an RSA, there are a number of atypical factors of the Symbicort submission that warrant additional consideration:

- The SYGMA clinical trial programme was clinician-instigated and driven. In support, the sponsor funded the SYGMA trials, registration and provided its health economic experience to lodge a reimbursement submission;
- The clinical need is long-standing and is not adequately addressed by any other PBS listed drug in either F1 or F2;
- Symbicort is TGA-registered for anti-inflammatory reliever therapy, an indication that would address the unmet need. It is rare for sponsors to pursue a PBAC submission to extend indications post-patent expiry. The sponsor of Symbicort, on the other hand, has remained active in working to provide care for asthma patients despite the patent status of Symbicort.

*For more detail on PBAC's view, see section 5 PBAC outcome.*

## **5 PBAC Outcome**

- 5.1 The PBAC recommended the Authority Required (STREAMLINED) listing of budesonide with formoterol for use as an anti-inflammatory reliever therapy administered as needed for adolescent and adult patients with mild asthma. The PBAC considered the concerns raised at the July 2019 meeting regarding the non-inferiority clinical claim and the mixed consumer comments from major asthma related organisations were adequately addressed in the minor resubmission and corresponding consumer comments.
- 5.2 The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of budesonide with formoterol would be acceptable if it were cost-minimised against low dose inhaled corticosteroid (ICS) maintenance regimen with short-acting acting beta2-agonist (SABA) as needed (ICS+SABA) on a drug cost per patient per day basis.
- 5.3 The PBAC noted the consumer comments from three key asthma related organisations (National Asthma Council Australia, Asthma Australia and The Lung Foundation), were in support of the requested listing for budesonide with formoterol.
- 5.4 The PBAC noted that the resubmission proposed a separate listing for use of budesonide with formoterol as an anti-inflammatory reliever therapy in mild asthma, in addition to the current (maintenance therapy) listing, and considered this was appropriate in the context of clear differentiation between indications. The PBAC agreed with the Secretariat's proposed changes to the requested listing, i.e. amending the PBS indication to "mild asthma", and removing the reference to maintenance and reliever therapy. The PBAC recommended that the sponsor's proposed administrative

advice (that only one prescription is permitted in a 12 month period) be removed, as this cannot be enforced by the Department of Human Services through a Streamlined Authority. The PBAC reiterated its July 2019 advice that the Committee considered that patients are likely to have more than one budesonide with formoterol inhaler in use at a time (paragraph 7.12, Symbicort, PSD, July 2019 PBAC meeting). As such, the PBAC recommended that the number of repeats be increased from 1 to 2.

- 5.5 The PBAC recalled the key clinical trial evidence presented in the July 2019 submission and the concerns around the primary outcomes for SYGMA 1 and SYGMA 2, i.e. well controlled asthma weeks (WCAW) and rate of severe exacerbations respectively. With respect to WCAW, the PBAC noted the concerns raised in the resubmission that this measure inherently biases against budesonide with formoterol when comparing to ICS+SABA. The PBAC considered that removal of the 'as needed' component improved the likelihood of patients receiving budesonide with formoterol achieving a WCAW, although the results continued to favour ICS+SABA. With respect to rate of severe exacerbations, the PBAC noted the sponsor's argument against the use of the 97.5% confidence interval (CI). In addition, the PBAC noted evidence from the Novel START and PRACTICAL trials supporting the use of budesonide with formoterol as required in mild asthma. On balance, the PBAC considered that the body of evidence supports the proposed listing.
- 5.6 The PBAC noted the resubmission's updated cost-minimisation analysis and considered that the change in expected market share from 93% and 7% to 60% and 40% for the Turbuhaler and Rapihaler respectively was appropriate. The PBAC advised that the cost-minimisation analysis should be based on AEMPs and equi-effective doses of 83.2 mcg of budesonide with 2.5 mcg of formoterol per day and 201 mcg of budesonide with 78.4 mcg of salbutamol per day.
- 5.7 The PBAC recalled that, in July 2019, the certainty around the financial estimates had been low, with the uptake rate and number of inhalers per year being key areas of concern raised by DUSC. The PBAC considered that, in addition to the market device split of 60% and 40% for the Turbuhaler and Rapihaler respectively proposed in the resubmission, it would be appropriate to assume an uptake rate of 25% in Year 1, 28% in Year 2, 40% in Year 3 and 42% in Years 4 to 6 (i.e. increased by 10% for Years 3-6 only) and that 3.042 inhalers (i.e. instead of 1.58 inhalers) would be used per patient per year. The PBAC considered that on this basis it was now reasonable to accept the financial estimates.
- 5.8 The PBAC noted the RSA proposed by the resubmission and the subsequent arguments for this approach in the pre-PBAC response . However, the PBAC considered that the uncertainty in the financial estimates would be more suitably addressed through determining the appropriate price based on a cost-minimisation analysis and revised assumptions for the estimates of use (see paragraph 5.7). On this basis, the PBAC advised that a weighted price across all budesonide with formoterol

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indications would be required to ensure the cost-effectiveness of budesonide with formoterol versus ICS+SABA for use as anti-inflammatory reliever therapy.

- 5.9 The PBAC advised that budesonide with formoterol is suitable for prescribing by nurse practitioners, as applies to the current PBS listing for budesonide with formoterol.
- 5.10 The PBAC advised that budesonide with formoterol should be exempt from the Early Supply Rule, as applies to the current PBS listing for budesonide with formoterol.
- 5.11 Under Section 101(3BA) of the *National Health Act 1953*, the PBAC advised that budesonide with formoterol should not be treated as interchangeable with any other drugs on an individual patient basis.
- 5.12 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because budesonide with formoterol is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over ICS+SABA, or address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.
- 5.13 The PBAC advised that this submission would not meet the criteria for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 6 Recommended listing

### 6.1 Add new item:

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of repeats	Proprietary Name and Manufacturer
BUDESONIDE + FORMOTEROL (EFORMOTEROL)					
budesonide 100 microgram/actuation + formoterol (eformoterol) fumarate dihydrate 3 microgram/actuation inhalation, 120 actuations	[new]	2	2	2	Symbicort Rapihaler 100/3 AstraZeneca Pty Ltd
budesonide 200 microgram/actuation + formoterol (eformoterol) fumarate dihydrate 6 microgram/actuation powder for inhalation, 120 actuations	[new]	1	1	2	Symbicort Turbuhaler 200/6 AstraZeneca Pty Ltd

Restriction Summary [new] / Treatment of Concept: [new]

Concept ID	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:

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	<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
	<b>Episodicity:</b> nil
	<b>Severity:</b> Mild
	<b>Condition:</b> asthma
new	<b>Indication:</b> Mild asthma
new	<b>Clinical criteria:</b> Patient must have asthma and require an anti-inflammatory reliever therapy
	<b>AND</b>
New [22302 admin advice]	<b>Clinical criteria:</b> Patient must not be on a concomitant single agent long-acting-beta-2-agonist (LABA)
	<b>AND</b>
9911	<b>Population criteria:</b>
9910	Patient must be aged 12 years or over
new	<b>Administrative Advice:</b> This drug is not PBS-subsidised for the treatment of chronic obstructive pulmonary disease (COPD) or for the treatment of allergen- or exercise-induced bronchoconstriction
21822	<b>Administrative Advice:</b> A LABA includes olodaterol, indacaterol, salmeterol, formoterol or vilanterol
new [24542 admin advice]	<b>Caution:</b> Device (inhaler) technique should be reviewed at each clinical visit and before initiating treatment with this medicine.

*This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.*

## **7 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.

## **8 Sponsor's Comment**

The sponsor had no comment.