6.03 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 submission requested an extension of the current 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 who are uncontrolled on short-acting beta2-agonist (SABA) as needed or controlled on a regimen of inhaled corticosteroid (ICS) maintenance plus SABA as needed. The submission applies to the Symbicort 200/6 Turbuhaler and the Symbicort 100/3 Rapihaler only. This was the first application to the PBAC for Symbicort in this population. Symbicort Turbuhaler was PBS-listed for patients who are symptomatic on ICS therapy or who are established on regular long acting beta2 agonist (LABA) and ICS therapy in February 2003 with Symbicort Rapihaler PBS-listed in December 2013.

1.2 The listing was requested based on a cost-minimisation analysis compared with ICS daily maintenance plus SABA as needed (ICS+SABA), and a cost-utility analysis compared with SABA as needed.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients aged ≥ 12 years with asthma who are uncontrolled on SABA or controlled on a regimen of ICS+SABA.
Intervention	Budesonide 200 mcg/actuation + formoterol 6 mcg/actuation powder for inhalation (Symbicort Turbuhaler 200/6) OR Budesonide 100 mcg/actuation + formoterol 3 mcg/actuation inhalation (Symbicort Rapihaler 100/3) an anti-inflammatory reliever used as needed for mild asthma.
Comparator	Primary: ICS single inhaler twice daily + SABA as needed (referred to as ICS+SABA). Secondary: SABA as needed (referred to as SABA).
Outcomes	Severe asthma exacerbations, medicine utilisation, ACQ-5 score, safety.
Clinical claim	The submission claimed that Symbicort used as needed in patients with mild asthma is: • Non-inferior to ICS+SABA in reducing severe asthma exacerbations and has a comparable safety profile. • Superior to SABA in reducing severe asthma exacerbations and has an equivalent safety profile.

Source: Table 1.1.1, p11 of the submission
ACQ-5 = asthma control questionnaire-5; ICS = inhaled corticosteroid; SABA = short-acting beta2-agonist

2 Requested listing

2.1 Amendments to the current PBS listing of Symbicort 200/6 Turbuhaler and Symbicort 100/3 Rapihaler for asthma proposed by the submission are shown in bold with strikethrough used for deletions. Suggestions proposed by the Secretariat to the requested listing are shaded in grey with strikethrough used for deletions and additions in italics.

Symbicort Turbuhaler 200/6

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
BUDESONIDE + FORMOTEROL, budesonide 200 microgram/actuation + formoterol fumarate dihydrate 6 microgram/actuation powder for inhalation	1	5	$44.64	SYMBICORT Turbuhaler 200/6 AstraZeneca Pty Ltd

PBS indication:	Asthma
Category/Program:	Authority Required (Streamlined)
Clinical criteria:	• ~~Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids~~; • **Patient must have asthma and require an anti-inflammatory reliever therapy** OR • Patient must have experienced frequent asthma symptoms while receiving treatment with oral or inhaled corticosteroids and require single maintenance and reliever therapy; OR • 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.
Population criteria:	Patient must be aged 12 years or over.
Note:	~~This product is not indicated for the initiation of treatment in asthma~~ This drug is not PBS-subsidised for the treatment of *chronic obstructive pulmonary disease (*COPD*)*. The patient must not be on a concomitant single long-acting-beta-2-agonist (LABA) A LABA includes olodaterol, indacaterol, salmeterol, formoterol or vilanterol

	Adherence to current treatment and device (inhaler) technique should be reviewed at each clinical visit and before 'stepping up' a patient's medication regimen. *Pharmaceutical benefits that have the brand DuoResp Spiromax 200/6 powder for inhalation, 120 actuations and pharmaceutical benefits that have the brand Symbicort Turbuhaler 200/6 powder for inhalation, 120 actuations are equivalent for the purposes of substitution.*

Symbicort Rapihaler 100/3

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
BUDESONIDE + FORMOTEROL, budesonide 100 microgram/actuation + formoterol fumarate dihydrate 3 microgram/actuation inhalation	2	5	$49.31	SYMBICORT Rapihaler100/3	AstraZeneca Pty Ltd

PBS indication:	Asthma
Category/Program:	Authority Required (Streamlined)
Clinical criteria:	• ~~Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids~~; • **Patient must have asthma and require an anti-inflammatory reliever therapy** OR • Patient must have experienced frequent asthma symptoms while receiving treatment with oral or inhaled corticosteroids and require single maintenance and reliever therapy; OR • 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.~~
Population criteria:	Patient must be aged 12 years or over.
Note:	~~This product is not indicated for the initiation of treatment in asthma~~ This drug is not PBS-subsidised for the treatment of *chronic obstructive pulmonary disease (*COPD*)*. The patient must not be on a concomitant single long-acting-beta-2-agonist (LABA) A LABA includes olodaterol, indacaterol, salmeterol, formoterol or vilanterol Adherence to current treatment and device (inhaler) technique should be reviewed at each clinical visit and before 'stepping up' a patient's medication regimen.

Source: Table 1.4.2, p19 of the submission

2.2 The requested change to the PBS restriction would extend the current PBS listings for Symbicort Turbuhaler 200/6 and Symbicort Rapihaler 100/3 for asthma by allowing these products to be used in an earlier line of therapy and to be used for the initiation of treatment in asthma.

2.3 The requested restriction appeared to be consistent with the proposed TGA indication.

2.4 The requested restriction was inconsistent with the PICO (Population, Intervention, Comparison and Outcome description) and trial populations, who were patients aged 12 years and over with asthma who are uncontrolled on SABA or controlled on a regimen of ICS+SABA. The requested listing does not explicitly mention that patients must be failed on SABA as needed or controlled on ICS+SABA. With the proposed wording of the PBS restriction, as needed Symbicort could be potentially used in the treatment-naïve mild-asthma patients. The trial populations presented in the

submission do not include treatment-naïve mild asthma patients. The Pre-Sub-Committee Response (PSCR) stated that the intention of the proposed changes to the PBS restriction wording was to allow Symbicort to be reimbursed as an alternative to ICS+SABA in patients requiring step 2 (i.e. an ICS) based on the National Asthma Council Australia (NAC) guidelines, and not for patients with very mild asthma that (under current NAC guidelines) should receive only a SABA. The PSCR stated that if Symbicort is accepted by the PBAC as being as effective as ICS+SABA, then the proposed restriction wording should reflect Symbicort and ICS+SABA having equitable access on the PBS for patients requiring step 2 therapy according to NAC guidelines.

2.5 The ESC noted that the current PBS restriction is generally in line with the NAC guidelines step 3 and above treatment and considered that the proposed PBS restriction appeared to be in line with step 2 of the NAC (2019) guidelines. The ESC noted that the guidelines emphasise that most patients with mild asthma would initiate treatment with ICS+SABA (i.e. step 2) rather than use SABA as needed monotherapy (step 1). The ESC considered that the patient population at step 2 of the NAC guidelines is broader than the trial population presented in the submission.

2.6 The proposed restriction is in line with the newly released Global Initiative for Asthma 2019 (GINA 2019) framework which has removed SABA as needed treatment in step 1 and now recommends as needed ICS-formoterol (e.g. Symbicort) use in both step 1 and 2 of the treatment algorithm.

2.7 DUSC noted that the TGA clinical evaluator's report (2nd round) indicates that Symbicort as needed may not be appropriate for prevention of allergen or exercise-induced bronchoconstriction, but the requested restriction did not exclude this population.

2.8 The ESC noted that Symbicort Turbuhaler 200/6 is interchangeable with DuoResp Spiromax 200/6 with these two products considered as brand equivalent ('a' flagged) for the purposes of substitution on the PBS. The ESC noted that the Symbicort Rapihaler 100/3 does not have an alternative product considered as brand equivalent listed on the PBS.

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

3 Background

Registration status

3.1 The submission was made under TGA/PBAC Parallel Process. The TGA submission applied to the Symbicort 200/6 Turbuhaler and the Symbicort 100/3 Rapihaler only. At the time of evaluation, the clinical evaluator's report (2nd round) was available. The clinical evaluator recommended approval of the indication: "Symbicort Turbuhaler is indicated for the treatment of asthma, to achieve overall asthma control, including

the relief of symptoms and the reduction of the risk of exacerbations. Symbicort is suitable for any asthma severity, where the use of inhaled corticosteroids is appropriate." Further, the clinical evaluator noted that TGA has previously considered that bridging between Symbicort Turbuhaler and Symbicort Rapihaler was already approved. It implied that Symbicort Rapihaler and Symbicort Turbuhaler at corresponding strengths (i.e., 100/3 and 200/6, respectively) would also be therapeutically equivalent in mild asthma. The PBAC noted that the Delegate's decision is expected on 13 September 2019.

3.2 The current TGA registered indication for the Symbicort 200/6 Turbuhaler and the Symbicort 100/3 Rapihaler is: "for the treatment of asthma where use of a combination (ICS and long acting beta-agonist) is appropriate. This includes: patients who are symptomatic on ICS therapy; patients who are established on regular long acting beta-agonist and ICS therapy. There are two alternative treatment regimens: Symbicort maintenance and reliever therapy; Symbicort maintenance therapy.

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

4 Population and disease

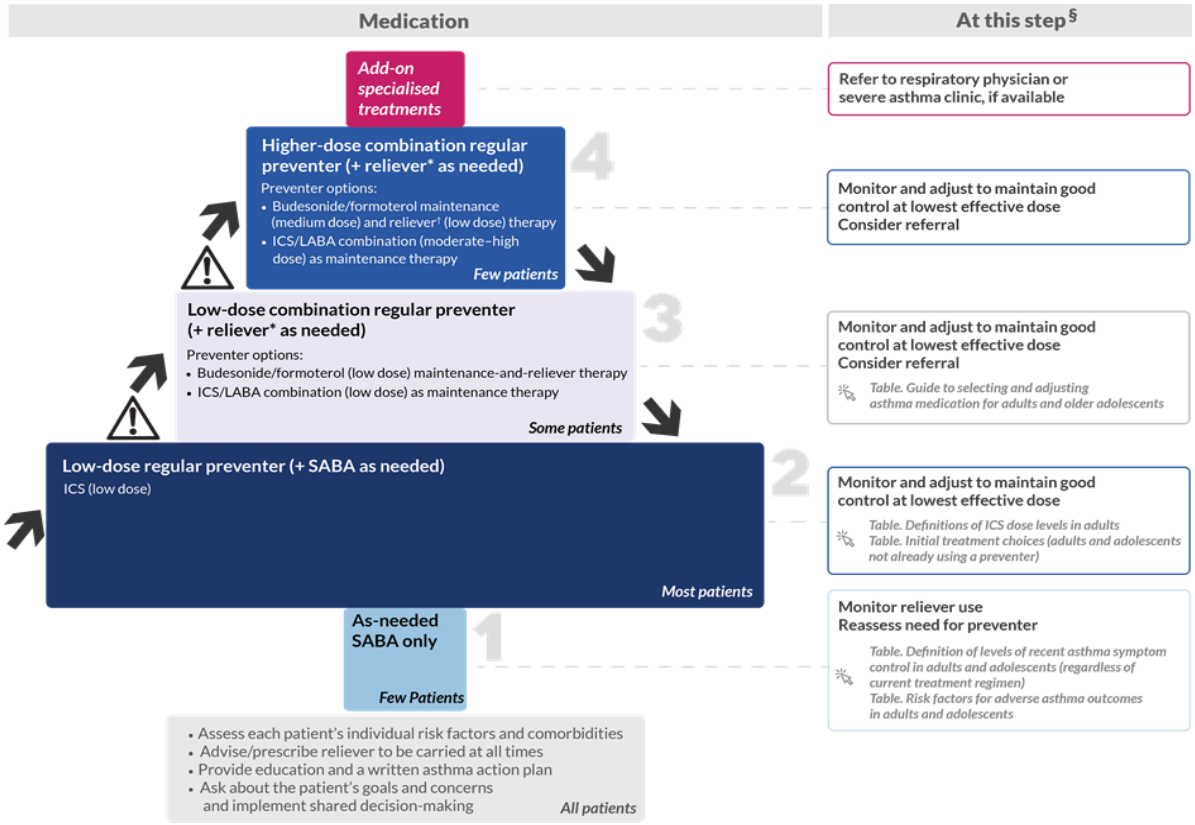
4.1 Asthma is a chronic inflammatory disorder of the airways with typical symptoms of recurrent episodes of wheezing, breathlessness, chest tightness and coughing. Asthma symptoms frequently cause sleeplessness, daytime fatigue, reduced activity levels, and school and work absenteeism.

4.2 Asthma severity is determined by the type and amount of treatment needed to maintain adequate symptom control, with more serious disease requiring a greater intensity of treatment. Based on the current NAC (2019) guidelines, a stepped treatment approach dependent on asthma control is central to asthma management, with the recommended treatments for adults and adolescents at each step presented below:

- Step 1: SABA monotherapy is appropriate for patients with symptoms less than twice a month and no flare ups that required oral corticosteroids (OCS) within previous 12 months. The ESC noted that, as of March 2019, revisions were made to the stepped approach algorithm to emphasise that most patients with mild asthma would initiate treatment with ICS+SABA and only a small proportion of patients should manage asthma with as-needed SABA monotherapy (see Figure 1).
- Step 2: A low dose ICS daily maintenance regimen is recommended for patients who do not meet the symptom control criteria at step 1. Based on the guidelines, most patients should initiate treatment on an ICS twice daily and SABA as needed (referred to as ICS+SABA).

- Step 3-5: ICS/LABA fixed dose combinations are reserved for patients who continue to have frequent episodes of asthma while receiving treatment with OCS or ICS+SABA.

Figure 1 Stepped approach to adjusting ASTHMA MEDICATION – Australian Asthma Guidelines (NAC)



Source: Figure 1, p 13 of the submission

4.3 For the proposed population in the PICO, patients aged ≥ 12 years with asthma who are uncontrolled on SABA or controlled on a regimen of low dose ICS+SABA, the current standard of care according to the NAC (2019) guidelines is a low dose ICS maintenance regimen plus SABA as needed. The PBAC agreed with the ESC that the PICO population is a subset of patients within step 2 of the NAC (2019) guidelines as treatment-naïve patients may also be eligible for step 2 treatment options.

Updated GINA 2019 Framework

4.4 During the evaluation period, GINA released an updated "Pocket Guide for Asthma Management and Prevention" in April 2019 (the full guidelines were not released during the period of evaluation). The updated guidelines included a major change to the GINA asthma treatment strategy for mild asthma. The change relates to step 1 and step 2 with the new recommendations presented below:

- Step 1: As needed low dose ICS-formoterol (off-label) as the preferred controller, with low dose ICS taken whenever SABA is taken (off-label) as the other controller option.

- Step 2: Daily low dose ICS plus as needed SABA OR as needed low dose ICS-formoterol (off-label) as the preferred controllers, with low dose ICS taken whenever SABA is taken (off-label) OR leukotriene receptor antagonists (LTRA) as the other controller options.

4.5 The major change was that SABA as needed treatment in step 1 is no longer recommended as over-use of SABA is associated with an increased risk of severe exacerbations, and dispensing of ≥ 12 canisters in a year is associated with increased risk of asthma-related death. Instead, GINA recommends that all adults and adolescents with asthma should receive ICS-containing controller treatment, to reduce the risk of serious exacerbations and to control symptoms. The ESC noted, as outlined above, low dose ICS-formoterol is stated as the preferred controller at step 1 of the GINA (2019) framework. The ESC noted that this change in recommendation is specific to ICS-formoterol due to the rapid onset of action of formoterol compared to other LABAs.

4.6 The ESC noted that the revised GINA framework states that the recommendation of ICS-formoterol as the preferred controller at step 1 was based on: indirect evidence from the SYGMA 1 trial (i.e. Symbicort compared with SABA-only treatment in patients eligible for step 2 therapy); that overuse of SABA as needed treatment is associated with an increased risk of severe exacerbations; and that adding ICS significantly reduces the risk of severe exacerbations.

4.7 For step 2 treatment, as needed ICS plus formoterol (off-label) is now added as an additional preferred controller alongside ICS+SABA which is the current standard of care in Australia. The guideline acknowledged that the evidence is only currently available for low dose budesonide with formoterol, but low dose beclometasone with formoterol could be potentially used in a similar way. The ESC noted that the guideline states that this change was based on evidence from the SYGMA 1 and SYGMA 2 trials.

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

5 Comparator

5.1 The submission nominated twice daily low dose ICS maintenance regimen with SABA as needed (ICS+SABA) as the main comparator. This is in line with step 2 treatment of NAC (2019) guidelines and GINA (2019) framework. The ESC considered that the nominated main comparator was appropriate.

5.2 The submission also nominated SABA as needed as the secondary comparator. The main rationale for the nomination was that a significant proportion of patients with mild asthma use SABA. In addition, the submission proposed that many patients were non-complaint with daily ICS and thus over-relied on SABA as needed. Therefore, the submission stated that Symbicort would replace currently PBS-listed SABA among this group of patients. For the population specified in the PICO of the submission (uncontrolled on SABA or controlled on a regimen of ICS+SABA), this would not be an

appropriate comparator because, in the absence of Symbicort being available on the PBS in the proposed population, patients uncontrolled on SABA would otherwise switch to ICS+SABA. The ESC considered the comparison with SABA may not be appropriate given the intention (as restated in the PSCR) that Symbicort be used at step 2 of the NAC guidelines, where an ICS is indicated.

5.3 However, with the recent update of the GINA framework, SABA as needed treatment is no longer recommended at step 1 and as such, patients at any disease severity would likely be initiated on Symbicort in place of SABA or would switch from SABA to Symbicort. The ESC noted that there was no clinical evidence presented to support the use of Symbicort in this population or to conduct an economic evaluation in this line of therapy.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (1), health care professionals (3) and organisations (3). Some of the comments described the benefits of treatment with Symbicort, including less reliance on short-acting reliever therapy and better control of asthma symptoms. However, the PBAC also noted the advice received from Asthma Australia, who raised concerns over 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.

Clinical trials

6.3 The submission was based on two head-to-head randomised trials (SYGMA 1 and 2) comparing Symbicort as needed with daily low dose ICS plus SABA as needed in patients with mild asthma aged 12 years or more. SYGMA 1 also included an additional SABA as needed only arm.

6.4 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
SYGMA 1	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 compared with SABA Turbuhaler 0.4 mg 'as needed' and with Pulmicort (budesonide) Turbuhaler 200 µg twice daily plus SABA Turbuhaler 0.4 mg as needed. O'Byrne PM, FitzGerald M, Bateman ED, et al. Inhaled combined budesonide plus formoterol as needed in mild asthma.	February 2018 *NEJM* 2018; 378:1865-76.
SYGMA 2	A 52-week, double blind, randomised, multi centre, phase III, parallel group study in patients 12 years and older with asthma, evaluating the efficacy and safety of Symbicort (budesonide/formoterol) Turbuhaler 160/4.5 µg 'as needed' compared with Pulmicort (budesonide) Turbuhaler 200 µg twice daily plus SABA Turbuhaler 0.4 mg 'as needed'. Bateman ED, Reddel HK, O'Byrne PM, et al. As needed budesonide formoterol versus maintenance budesonide in mild asthma.	February 2018 *NEJM* 2018; 378:1877-87.

Source: Table 2.2.1, p24 of the submission
SABA = short-acting beta2 agonists

6.5 Patients in both trials were enrolled if they were aged 12 years or older and were uncontrolled on SABA or controlled on a regimen of ICS+SABA. They were assessed as eligible for step 2 treatment (daily low dose ICS plus SABA as needed) as per GINA (2012) framework.

6.6 The trial populations were consistent with the proposed population in the PICO. However, the trial populations were a subset of the population eligible to receive treatment at step 2 of the NAC (2019) guidelines, as treatment-naïve patients may also be eligible for step 2 treatment options. Further, the trial populations were narrower than the requested PBS restriction, where Symbicort may be used at any asthma severity. The appropriate trial population to support the requested restriction would be all patients with mild asthma. However, no evidence was presented to support the use of Symbicort, compared to SABA as needed, as initial therapy in mild asthma patients naïve to treatment. As outlined above in paragraph 2.4, the PSCR stated the intention was to use Symbicort in patients who have mild asthma and require an ICS, and not for patients with very mild asthma that, under current NAC guidelines, should receive SABA alone. In addition, the PSCR argued that in the Australian context where SABA is available over the counter it would be extremely unlikely to find a patient with a diagnosis of asthma who had never received a SABA. The ESC noted that according to step 2 of the NAC guidelines most patients would initiate treatment with ICS+SABA rather than SABA as needed monotherapy. Hence, the ESC considered that data on treatment-naïve patients would be informative, although the ESC acknowledged that it may be difficult to collect this data in the Australian population due to the existing over the counter SABA market.

6.7 The participants were generally well balanced between treatment arms in terms of baseline demographics, disease severity and pre-study treatment. The PBAC noted

that there were substantial differences in smoking status of the trial populations at baseline and Australian population (SYGMA 1 smoking status: never 87.0%, former 10.3%, current 2.7%; SYGMA 2 smoking status: never 84.3%, former 13.1%, current 2.6%; ABS National Health Survey, 2014–15[1] people over 18 with asthma smoking status: never 47.5%, former 35.8%, current 15.4%). The key features of the direct randomised trials are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Key Outcomes	Use in modelled evaluation
Symbicort vs. ICS+SABA						
SYGMA 1	3849	R, MC, DB, PG 52 weeks	Low	Adolescents and adults, 12 year or more, mild asthma	WCAW, Rate of severe exacerbations, ACQ-5, utilisation of ICS	Not used
SYGMA 2	4215	R, MC, DB, PG 52 weeks	Low	Adolescents and adults, 12 year or more, mild asthma	Rate of severe exacerbations, ACQ-5, utilisation of ICS	Not used
Symbicort vs. SABA						
SYGMA 1	3849	R, MC, DB, PG 52 weeks	Low	Adolescents and adults, 12 year or more, mild asthma	WCAW, severe exacerbations, ACQ-5, utilisation of ICS	Rate of severe and moderate exacerbations

Source: Compiled during the evaluation based on p29-34 of the submission
ACQ-5= asthma control questionnaire (5 items); DB = double blind; MC = multi-centre; R = randomized; PG = parallel group; WCAW = well-controlled asthma weeks

6.8 The PBAC noted the difference in primary outcomes between the trials, that is, well-controlled asthma weeks (WCAW) for SYGMA 1 and rate of severe exacerbations for SYGMA 2. With respect to SYGMA 1, the PBAC noted that the primary outcome was WCAW for the comparison of Symbicort versus SABA, while the comparison of Symbicort versus ICS+SABA (for WCAW) was a secondary outcome.

6.9 The submission presented the rate of severe asthma exacerbations and the change from baseline in asthma symptom score (ACQ-5) as the key outcomes of interest.

6.10 The key outcomes of interest presented in the submission were previously considered to be clinically relevant by the PBAC in submissions related to asthma (Paragraph 8, Symbicort March 2007 PSD & Paragraph 6.7, Omalizumab July 2016 PSD). It is arguable whether ACQ-5, instead of severe asthma exacerbation, should be the more appropriate primary outcome in this group of patients with mild asthma. Total ICS dose from SYGMA 2 was used in the cost-minimisation analyses.

6.11 Table 4 summarises the definitions and methods of analysis for the outcomes presented in the submission. Overall, the statistical methods were largely appropriate.

[1] Australian Institute of Health and Welfare. Asthma, associated comorbidities and risk factors. Canberra: AIHW; 2016.

Table 4: Definition of the outcomes, unit of measure and method of analysis

Outcome	Definition	Unit of measure	Method of analysis
Asthma exacerbations			
Annual severe asthma exacerbations	Deterioration of asthma requiring one or more of the following: (i) use of OCS for 3 days or more (ii) in-patient hospitalisation or (iii) Emergency Department visit that required systemic steroids.	Annual exacerbation rate	Exacerbations were analysed using negative binomial model adjusted for randomised treatment, pre-study treatment group and region and number of severe adverse events in prior 12 months (0 or ≥ 1) and offset for follow-up time. It was expressed as rate ratio (RR) with corresponding 1-sided 95% CI.
Moderate exacerbation	Deterioration of asthma requiring a change in treatment i.e. initiation of prescribed ICS to avoid progression of the worsening of asthma to severe exacerbation.	Annual exacerbation rate	
Asthma symptom control			
ACQ-5	ACQ-5 includes five items[a] about symptoms based on a 7-day recall period: measured on a 7-point scale from 0 (well controlled) to 6 (extremely poorly controlled). Responders were defined as patients with an improvement of ≥ 0.5 from baseline for the total ACQ score at end of treatment (52 weeks).	Mean score	ACQ-5 change score were analysed with the use of a mixed model for repeated measures adjusted for treatment group, pre-study treatment, region, baseline FEV1, visit, and visit by randomized treatment group interaction.
Well-controlled asthma weeks (WCAW)	A composite measure. A week was considered well controlled if the following criteria were met: (i) Two or more from the following: no more than 2 days with a daily asthma symptom score >1; no more than 2 days of as needed medication use, up to a maximum of 4 occasions per week (multiple occasions per day should be regarded as separate occasions); morning PEF ≥ 80% of PN every day (ii) Both of the following criteria are fulfilled: no night time awakenings due to asthma; no additional inhaled and/or systemic GCS treatment due to asthma	Mean % of weeks	Average portion of WCAW analysed by a repeated measure, logistic regression with randomised treatment, pre study treatment, region and study week as fixed effects, with study week included as a categorical variable. Estimated as ORs of achieving a WCAW and corresponding 95% CIs
Utilisation of medications			
As needed medication	SYGMA 1 •Symbicort in the Symbicort arm •SABA in the ICS+SABA and SABA arms SYGMA 2: •Symbicort in the Symbicort arm •SABA in the ICS+SABA arm	Mean days	Summary statistics presented and change from baseline analysed. Changes from baseline and free days were analysed using covariance (ANCOVA)
Maintenance medication	SYGMA 1: •Placebo in the Symbicort and SABA arms •Budesonide in the ICS+SABA arm SYGMA 2: •Placebo in the Symbicort arm •Budesonide in the ICS+SABA arm	Mean daily dose	Compliance with twice daily calculated as total actual inhalations divided by total expected inhalations over the randomised treatment period multiplied by 100. Summary statistics presented
ICS controller use and total ICS load	Budesonide component in Symbicort and ICS+SABA arm. Any additional prescribed ICS	Mean daily dose	The percentage of days an ICS controller was used was averaged over the treatment period and analysed using ANCOVA

Outcome	Definition	Unit of measure	Method of analysis
Additional steroids (ICS and GCS)	All inhaled and OCS prescribed excluding study treatment	Mean days	Summary statistics presented for total time to administration of additional steroids for asthma was calculated as the time from first dose of IP until the start date of administration of additional steroids for asthma

Source: Table 2.4.3 of the submission & p41 CSR SYGMA 1
ACQ-5 = asthma control questionnaire (5-item version); FAS = full-set analysis; FEV1 = forced expiratory volume in 1 second; GCS = glucocorticoids; ICS = inhaled corticosteroid; SABA = short-acting beta2-agonist; OCS = oral corticosteroid; PEF = Peak expiratory flow; PN = predicted normal
[a] Included frequency of night-time awakening, severity of asthma symptoms upon awakening, extent of activity limitations, frequency of shortness of breath, and frequency of wheezing.

6.12 To demonstrate superiority to comparators, the submission specified minimally clinically important differences (MCID) and non-inferiority margins for the key outcomes. These values and their rationale are summarised in Table 5.

Table 5: Proposed MCID values and non-inferiority margins for the key outcomes

Proposed MCID	Proposed Non-inferiority margin	Submission's rationale
Reduction in severe asthma exacerbations		
≥ 20% difference in reduction in the annual rate of severe asthma exacerbations	Non-inferiority was declared when the upper 95% CI of the exacerbation rate ratio (Symbicort vs ICS+SABA) was < 1.20	The MCID was derived based on the expected exacerbation rates reported in the START and GOAL trials, which were conducted among patients with mild asthma and had a similar definition of severe exacerbation. The non-inferiority margin was based on the advice from an expert panel to AstraZeneca after amendment of trial design from superior to non-inferior.
Asthma symptoms (ACQ)		
-0.5 points change in the ACQ-5 from baseline	Non-inferiority declared when the upper 95% CI of change in ACQ-5 score was less than 0.5 points	The submission proposed that the MCID for ACQ-5 is globally accepted for asthma developed by the American Academy of Allergy Asthma and Immunology (AAAAI) (Schatz 2009).

Source: Compiled from p38 - 39 & Table 2.4.4 on p38 of the submission
ACQ-5 = Asthma Control Questionnaire 5-item Version; CI = confidence interval; ICS = inhaled corticosteroids; MCID = minimally clinical important difference; SABA = short-acting beta2-agonist; START = Inhaled Steroid Treatment as Regular Therapy; GOAL = Gaining Optimal Asthma control

6.13 The MCID proposed for ACQ-5 score was developed by the American Academy of Allergy Asthma and Immunology (AAAAI) (Schatz 2009) for not well-controlled asthma based on ≥ 1.5 on the ACQ. This was appropriate given the mean ACQ scores at baseline were generally >1.5. The PBAC has previously accepted a reduction of ≥ 0.5 ACQ total score as clinically meaningful for severe asthma (paragraph 7.5, tiotropium July 2015 PSD).

6.14 The proposed MCID of 20% between-group difference in reduction on severe exacerbations (based the results of the START (Inhaled Steroid Treatment as Regular

Therapy) and GOAL (Gaining Optimal Asthma control)) trials was not well justified. The PSCR stated that that there is no commonly accepted MCID in the literature for the reduction in severe asthma exacerbations and no previously accepted MCID by the PBAC that is relevant to both the trial population and the proposed indication. The ESC noted that the frequency of severe exacerbations was not overly common in the proposed PBS population. The ESC considered that, in terms of clinical relevance, smaller than a 20% reduction in severe exacerbation rates may represent a clinically meaningful difference, given the seriousness of the exacerbations.

6.15 The SYGMA 2 trial was initially designed as a superiority trial. However, a pre-specified sample size review revealed that the sample size was insufficient to demonstrate superiority, due to a less than anticipated exacerbation rate and a higher than expected adherence to maintenance treatment. As a result, a protocol amendment was made to change the trial objective from demonstrating superiority to non-inferiority. In such instances EMA guidelines recommend that if one-sided confidence intervals are used they should be used with a coverage probability of 97.5%.[2] The submission used a coverage probability of 95%. The ESC considered that use of the wider confidence interval would have been more appropriate. Further, the ESC noted that no results from per-protocol analyses were presented in the trials, which would be informative in non-inferiority trials.

Comparative effectiveness

Asthma exacerbations

6.16 Table 6 presents the results for the endpoints 'severe' annual exacerbation rates (SYGMA 1 and SYGMA 2) and 'moderate or severe' (SYGMA 1 only) annual exacerbation rates.

Table 6: Annual rate of asthma exacerbations (Full analyses set)

Trial	Symbicort		ICS+SABA			SABA		
	N	Annual rate (95% CI)	N	Annual rate (95% CI)	Rate Ratio (95% CI)[a]	N	Annual rate (95% CI)	Rate Ratio (95% CI)[a]
Severe asthma exacerbations								
SYGMA 1	1277	0.07 (0.06, 0.09)	1282	0.09 (0.07, 0.11)	0.83 (0.59,1.16)	1277	0.20 (0.16, 0.24)	**0.36 (0.27,0.49)**
SYGMA 2	2084	0.11 (0.10,0.13)	2083	0.12 (0.10,0.14)	0.97 (1.16)[b] 0.97 (1.20)[c]	-	-	-
Moderate or severe asthma exacerbations								
SYGMA 1	1277	0.14 (0.12, 0.17)	1282	0.15 (0.13, 0.18)	0.95 (0.74,1.21)	1277	0.36 (0.31, 0.42)	**0.40 (0.32,0.49)**

Source: Table 2.5.1, p40 of the submission & Table 30, p96 CSR3_SYGMA2
Bold = statistically significant; CI = confidence interval; ICS = inhaled corticosteroid; SABA = short-acting beta2-agonist

[2] 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

[a] Rate ratio are reported with Symbicort as a reference
[b] 1-sided upper 95% CI
[c] 1-sided upper 97.5% CI

Symbicort versus ICS+SABA

6.17 In SYGMA 1, no significant difference in annual rate of severe asthma exacerbations was detected for Symbicort and ICS+SABA arms (rate ratio (RR) = 0.83, 95% CI: 0.59, 1.16). Based on nominated MCID of 20%, the submission claimed that non-inferiority criteria were met because the annual severe exacerbation rate was 17% (less than 20%). However, a non-inferiority margin was not defined in SYGMA 1.

6.18 Similarly, no significant difference in the annual rate of severe asthma exacerbations between Symbicort and ICS+SABA arms (RR = 0.97, 1-sided upper 95% CI: 1.16) was reported in SYGMA 2. The submission claimed that non-inferiority was met because the 1-sided 95% CI for the rate ratio was less than 1.2, the nominated non-inferiority margin. However, the EMA recommend that when switching the trial objective from superiority to non-inferiority as occurred in SYGMA 2, and using one-sided confidence intervals, a 97.5% coverage probability should be used. Using the EMA recommendation the claim of non-inferiority was not met as the 1-sided upper 97.5% confidence interval rate ratio was 1.2. The PSCR argued that the analysis using a 2.5% 1-sided test was not the primary analysis; it was only a supportive analysis. The PSCR argued that the upper confidence interval fractionally exceeded the non-inferiority margin (RR 0.97; 97.5% upper CI 1.202) and that that focusing on this one supportive analysis is inappropriately selective. The ESC considered that the results were not very robust as the upper limit of the confidence interval was 1.16 (95% CI) in the primary analysis and 1.20 (97.5% CI) in the supportive efficacy analysis.

Symbicort versus SABA

6.19 SYGMA 1 reported a statistically significant and clinically meaningful reduction of both annual 'severe asthma exacerbations' and 'moderate or severe asthma exacerbations' events favouring Symbicort.

<u>Asthma symptom control</u>

6.20 Table 7 and 8 presents the results for asthma symptoms based on the ACQ-5 and WCAW.

Table 7: Results for ACQ-5 (Full analyses set)

Trial	Symbicort		ICS+SABA			SABA		
	N	LSM (95% CI)	N	LSM (95% CI)	LSM difference (95% CI)	N	LSM (95% CI)	LSM difference (95% CI)
SYGMA 1	1241	-0.33 (-0.36, -0.29)	1237	-0.48 (-0.51, -0.44)	**0.15 (0.10, 0.20)**	1225	-0.17 (-0.21, -0.14)	**-0.15 (-0.20, -0.11)**
SYGMA 2	1963	-0.35 (-0.38, -0.32)	1947	-0.46 (-0.49, -0.43)	**0.11 (0.07, 0.15)**	-	-	-

Source: Table 2.5.3, p42 of the submission
ACQ-5 = asthma control questionnaire 5-item Version; **Bold** = statistically significant; CI = confidence interval; LSM= least squared mean

Table 8: Results for WCAW (Full analyses set)

Trial	SYMBICORT (N=1269)			ICS+SABA (N=1279)			SABA (N=1272)		
	N	Mean % of WCAW per patient	OR (95% CI)	N	Mean % of WCAW per patient	OR (95% CI)	N	Mean % of WCAW per patient	OR (95% CI)
SYGMA 1	1269	34.4	-	1279	44.4	0.64 (0.57,0.73)	1272	31.1	**1.14 (1.0, 1.30)**

Source: Table 2.5.3, p42 of the submission.
Bold = statistically significant (reported p=0.046); CI = cconfidence interval; ICS= inhaled corticosteroid; LS = least squared; OR = odds ratio; WCAW = well controlled asthma weeks

Symbicort versus ICS+SABA

6.21 Both SYGMA trials detected statistically significant differences in the change from baseline in the ACQ-5 score in favour of ICS+SABA compared to the Symbicort. However, the differences were not clinically meaningful as the changes in ACQ-5 scores were lower than the nominated MCID (i.e. -0.5) which has been previously accepted by the PBAC as clinically meaningful for severe asthma (paragraph 7.5, tiotropium July 2015 PSD). 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.

6.22 The submission also presented results for WCAW from SYGMA 1. Symbicort had 36% lower odds of achieving a WCAW compared to ICS+SABA during the study period (34.4% vs. 44.4%, Odds Ratio (OR) 0.64, 95% CI: 0.57, 0.73). Although there was no MCID nominated for the outcome, the nearly 40% difference may represent a meaningful difference for patients. 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. 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.

Symbicort versus SABA

6.23 SYGMA 1 showed a statistically significant, but not clinically meaningful, difference in the change from baseline in the ACQ-5 score in favour of Symbicort. In addition, SYGMA 1 also reported Symbicort had 14% greater odds of achieving a WCAW compared to SABA during the study period (OR 1.14; 95% CI: 1.00, 1.30).

Utilisation of medications

6.24 Table 9 presents the utilisation of ICS and OCS during the study period.

Table 9 Utilisation of ICS and systematic OCS (Full analyses set)

	SYGMA 1			SYGMA 2	
	Symbicort	**ICS+SABA**	**SABA**	**Symbicort**	**ICS+SABA**
	N = 1277	N = 1282	N = 1277	N = 2089	N = 2087
ICS use (daily ICS, mcg)					
IP: Mean (SD) Median	74.4 (81.8) 45.5	251.9 (71.3) 271.8	NA	82.5 (87.5) 52.5	200.5 (94.1) 213.8
Total[a]: Mean (SD) Median	80.5 (90.4) 48.3	259.5 (81.6) 276.2	22.6 (68.6) 0.0	83.2 (87.8) 52.9	201.0 (94.2) 214.1
Mean number 'rescue' inhalations/day	0.47	0.39	0.58	0.52	0.49
OCS use					
No. of patients who had any	71	78	156	179	186
Mean (SD) days	6.55 (3.45)	6.41 (3.58)	7.93 (6.52)	7.56 (5.48)	6.72 (3.89)
Median	6.00	6.00	6.00	6.00	6.00
ICS controller use days (%), ANCOVA model					
	N = 1276	N = 1281	N = 1273	N = 2089	N = 2084
Mean (95% CI)	30.91 (29.68, 32.13)	85.76 (84.54, 86.98)	5.78 (4.56, 7.01)	30.45 (29.20,31.70)	67.92 (66.67, 69.17)
Mean difference (95% CI)	-	**-54.85** **(-56.58, -53.13)**	**25.12** **(23.4, 26.85)**	-	**-37.48** **(-29.18, -35.77)**

Source: Table 2.5.4 and 2.5.5, p43 of the submission
Bold = statistically significant; CI = confidence interval; ICS = inhaled corticosteroids; IP = investigation product; OCS = oral corticosteroid; SABA = short-acting beta2-agonist; SD = standard deviation
[a] Total = ICS administered as IP as well as any additional ICS prescribed.

Symbicort versus ICS+SABA

6.25 In both SYGMA trials, the total number of patients who took OCS treatment and the mean number of 'rescue' inhalations per day were comparable between the Symbicort and ICS+SABA arms. However, both the use of investigational ICS (74.4 mcg versus 251.9 mcg in SYGMA 1 and 82.5 mcg versus 200.5 mcg in SYGMA 2, respectively) and total ICS (80.5 mcg versus 259.5 mcg in SYGMA 1 and 83.2 mcg versus 201.0 mcg in SYGMA 2, respectively) were lower in the Symbicort arm compared to ICS+SABA arm. Similarly, the mean percentage of ICS controller use days was 55% and 37% lower in Symbicort arm compared to ICS+SABA arm in SYGMA 1 and 2, respectively. The ESC noted that the asthma exacerbation and symptom control outcomes reported for Symbicort were achieved with a lower level of ICS use than reported in the ICS+SABA arms of the SYGMA 1 and SYGMA 2 trials. The ESC considered that the finding that similar levels of control are achieved with Symbicort with lower levels of ICS use may be particularly beneficial for adolescents and pregnant women with mild asthma.

6.26 Patients in SYGMA 1, but not in SYGMA 2, were sent electronic reminders to comply with daily ICS maintenance therapy. Therefore, SYGMA 2 might be more reflective of a real world scenario of compliance with maintenance ICS than the compliance levels reported in SYGMA 1.

Symbicort versus SABA

6.27 The number of patients who took OCS for asthma in the Symbicort arm was approximately half that in the SABA arm.

Comparative harms

6.28 A summary of the adverse events reported in trials SYGMA 1 and SYGMA 2 are presented in Table 10. There were no noteworthy differences in the adverse-event profile between the treatments, except that any adverse events were more frequent with SABA compared with Symbicort.

6.29 Upper respiratory tract infection and viral upper respiratory tract infection were the most commonly reported adverse events in the Symbicort and ICS+SABA/SABA arms of both trials.

Table 10: Summary of key adverse events in the trials

	Symbicort	ICS+SABA	SABA	RD vs. ICS+SABA (95% CI)	RD vs. SABA (95% CI)
SYGMA 1					
N	1277	1282	1277	-	-
Any AE, n (%)	485 (38)	512 (40)	545 (43)	-0.02 (-0.06, 0.02)	**-0.05 (-0.08, -0.01)**
Any serious AE, n (%)	38 (3)	37 (3)	50 (4)	0.00 (-0.01, 0.01)	-0.01 (-0.02, 0.00)
AE leading to discontinuation, n (%)	10 (1)	15 (1)	37 (3)	-0.00 (-0.01, 0.00)	-0.02 (-0.03, 0.01)
Deaths, n (%)	0	2 (<1%)	0	-	-
AEs of special interest					
Any β2-agonist related AEs, n (%)	50 (4)	49 (4)	50 (4)	*0.00 (-0.01, 0.02)*	*0.00 (-0.02, 0.02)*
Any steroid class related AEs, n (%)	13 (1)	19 (2)	14 (1)	*0.00 (-0.01, 0.00)*	*0.00 (-0.01, 0.01)*
SYGMA 2					
N	2089	2087	-	-	-
Any AE, n (%)	887 (43)	919 (44)	-	-0.02 (-0.05, 0.01)	-
Any serious AE, n (%)	66 (3)	73 (4)	-	-0.00 (-0.01, 0.01)	-
Leading to discontinuation, n (%)	14 (1)	23 (1)	-	-0.00 (-0.01, 0.00)	-
Deaths, n (%)	1 (<1)	1 (<1)	-	-	-
AEs of special interest					
Any β2-agonist related AEs, n (%)	103 (5)	96 (5)	-	*0.00 (-0.01, 0.02)*	-
Any steroid class related AEs, n (%)	34 (2)	38 (2)	-	*0.00 (-0.01, 0.01)*	-

Source: Table 2.5.8, 2.5.9 & 2.5.12, p45-48 of the submission

AE = adverse event; **Bold**= statistically significant; CI = confidence interval; ICS = inhaled corticosteroid; RD = risk difference; SABA = short-acting beta2-agonists

Benefits/harms

6.30 The ESC noted that, as there were no significant differences reported between Symbicort and ICS+SABA, a benefits harms table was not presented.

6.31 A summary of the comparative benefits and harms for Symbicort versus SABA are presented in Table 11.

Table 11: Summary of comparative benefits and harms for Symbicort and SABA

Trial	Symbicort n/N	SABA n/N	RR (95% CI)	Event rate/100 patients/year		RD (95% CI)
				Symbicort	SABA	
Benefits						
Rate of severe exacerbations						
SYGMA 1	77/1277	188/1277	**0.36 (0.27, 0.49)**	6.02	14.72	**-0.09 (-0.11, -0.06)**
Asthma Control Questionnaire: change from baseline (LSM)						
	Symbicort			**SABA**		**LSM difference: Symbicort vs. SABA (95% CI)**
	N	**Mean Δ baseline LSM**	**(95% CI)**	**N**	**Mean Δ baseline LSM**	**(95% CI)**
SYGMA 1	1241	-0.33	(-0.36, -0.29)	1225	-0.17	(-0.21, -0.14)	**-0.154 (-0.203, -0.105)**
Harms						
	Symbicort n/N	**SABA n/N**	**RR (95% CI)**	**Event rate/100 patients per year**		**RD (95% CI)**
				Symbicort	**SABA**	
Upper respiratory tract infection						
SYGMA 1	71/1277	76/1277	0.93 (0.68, 1.28)	5.55	5.95	0.00 (-0.02, 0.01)
Viral upper respiratory tract infection						
SYGMA 1	75/1277	79/1277	0.95 (0.70, 1.29)	5.87	6.18	0.00 (-0.02, 0.02)

Source: Table 2.5.1, 2.5.3 and 2.5.11, p40,42,47 of the submission

Bold = statistically significant; CI = confidence interval; LSM = least squared mean; RD = risk difference; RR = rate ratio; SABA = short-acting beta2-agonist

6.32 On the basis of the direct comparison evidence presented by the submission, for every 100 patients treated with Symbicort in comparison to SABA and over a 1-year duration:

- approximately 64 fewer patients would have a severe asthma exacerbation (flare-up). The submission considered that an improvement of 20 fewer patients experiencing a severe exacerbation was clinically meaningful.

6.33 On the basis of the direct comparison evidence presented by the submission, for every 100 patients treated with Symbicort in comparison to SABA and over a 1-year duration:

- there would be no difference in the proportion of patients who developed upper respiratory tract infection; and
- there would be no difference in the proportion of patients who developed a viral upper respiratory tract infection.

Clinical claim

6.34 The 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.

6.35 The therapeutic claim of non-inferiority in terms of comparative effectiveness versus ICS+SABA may not be supported by the evidence presented because:

- non-inferiority in the SYGMA 2 trial was claimed as the one-sided 95% CIs of the rate ratio for severe asthma exacerbation was less than the nominated non-inferior margin of <1.20. However, when using the one-sided 97.5% CI for non-inferior trials as recommended by EMA, the non-inferiority margin of 1.20 was not met.
- SYGMA 1 was designed as a superiority trial, and hence no non-inferiority margin was specified. The submission claimed non-inferiority based on the non-significant difference in severe asthma exacerbations between Symbicort and ICS+SABA, and the upper 95% CIs was less than the MCID (i.e. 20%).

6.36 The PSCR argued that the analysis using a 2.5% 1-sided test was not the primary analysis and that that focusing on this one supportive analysis is inappropriately selective. The ESC considered that the data used to support the claim of non-inferior comparative effectiveness was not very robust as the upper limit of the confidence interval was 1.16 (95% CI) in the primary analysis and 1.20 (97.5% CI) in the supportive efficacy analysis. The ESC acknowledged that the treatment effect was generally consistent across the treatment arms in this comparison. However, the ESC considered that the Australian population for which Symbicort is proposed to be used is likely to be a population with milder asthma compared to the populations included in the SYGMA trials as the Australian setting would include treatment-naïve patients.

6.37 The ESC agreed with the evaluation that the claim of comparable safety versus ICS+SABA as needed was reasonable.

6.38 The submission also claimed that Symbicort used as an anti-inflammatory reliever, as needed, in patients with mild asthma is superior to SABA as needed in terms of comparative effectiveness and non-inferior in terms of safety.

6.39 Although the superiority claim versus SABA appeared to be supported by the evidence presented, the evidence was not relevant for this comparison as the trial population was inappropriate. The appropriate population for the comparison should be all patients with mild asthma including those who are treatment-naïve and eligible for step 2 treatment according to the NAC (2019) guidelines. However, the SYGMA trials only included a subset of patients eligible for step 2 treatment (patients with mild asthma uncontrolled on SABA or controlled on ICS+SABA). No trials of asthma patients naïve to treatment were presented in the submission to support the claim. Under the trial population presented in the submission, the results are highly likely to be biased

towards Symbicort, as the included patients have already failed SABA as needed therapy and should all be on ICS+SABA therapy. The ESC agreed with the evaluation that the evidence presented for the comparison with SABA may not be relevant given the intention that Symbicort be used at step 2 of the NAC guidelines, which includes patients who are treatment-naïve. In addition, although the PSCR stated that Symbicort is not intended for use in patients at step 1 of the NAC guidelines, the ESC considered that the lack of data in treatment-naïve patients raised concerns regarding the effects of potential use in those with very mild asthma (symptoms less than twice per month). While it is unknown, the ESC considered it likely that the treatment effects of Symbicort in patients with very mild asthma would be similar to those of SABA.

6.40 The ESC agreed with the evaluation that the claim of non-inferior safety versus SABA as needed was reasonable.

6.41 The PBAC considered that the claim of non-inferior comparative effectiveness versus ICS+SABA was not adequately supported by the data. The PBAC considered that the claim of superior comparative effectiveness versus SABA was not adequately supported by the data as SABA is not a relevant comparator for the trial population and proposed indication.

6.42 The PBAC considered that the claim of non-inferior comparative safety (versus both ICS+SABA and SABA only) was reasonable.

Economic analysis

6.43 The submission presented two economic analyses: a cost-minimisation approach comparing Symbicort and ICS+SABA; and a cost-utility analysis comparing Symbicort to SABA.

Cost-minimisation analysis

6.44 The cost-minimisation analysis presented in the submission comparing Symbicort with ICS+SABA was only reasonable if the non-inferiority of Symbicort versus ICS+SABA was considered established. The ESC noted that the SYGMA 1 trial was designed as a superiority trial and expressed concern with the use of studies not specifically designed to show the equivalence of treatments as the basis for a cost-minimisation analyses. The ESC also considered that the claim of non-inferiority based on the annual rate of severe asthma exacerbations was borderline based on the 97.5% confidence interval recommended by EMA. The PBAC considered that due to concerns regarding the claim of non-inferiority a cost-minimisation analysis would only be appropriate if it was sufficiently confident that the cost of Symbicort to the health system is, at most, equivalent to ICS+SABA.

6.45 The key components and assumption of cost-minimisation analysis are presented in Table 12.

Table 12: Key components and assumptions of the cost-minimisation analysis

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on the SYGMA 1 and SYGMA 2 trials, effectiveness was assumed to be non-inferior to ICS+SABA. This was reasonable if the non-inferiority of Symbicort versus ICS+SABA was considered established.
Therapeutic claim: safety	Based on the SYGMA 1 and SYGMA 2 trials, safety was assumed to be non-inferior to ICS+SABA. This was reasonable.
Evidence base	2 direct head-to-head trials: SYGMA 1 and SYGMA 2
Equi-effective doses	Based on SYGMA 2 trial total mean daily ICS dose: 83.2 mcg/day of budesonide[a] in Symbicort Turbuhaler 200/6 = 201.0 mcg/day budesonide + 196 mcg/day terbutaline which is equivalent to 49 mcg/day (78.4 mcg per day)[b] salbutamol. The ICS used in the SYGMA trials, budesonide, was used in the CMA. Terbutaline was the SABA used in the SYGMA trials. However, salbutamol was used in the CMA. The submission stated that salbutamol is the most commonly used SABA in Australia.
Direct medicine costs	Based on equi-effective doses, per year the cost of Symbicort was more than ICS+SABA. Asthma is a chronic illness and the costs are presented per patient per year. The submission's claim of cost-minimisation was not met.
Other costs or cost offsets	Not applicable

Source: Table 3.1, p54 in the submission

CMA = cost minimisation analysis; ICS = inhaled corticosteroid; SABA = short-acting beta2-agonist

[a] 83.2 mcg/day of budesonide and 2.5 mcg/day of formoterol in Symbicort Turbuhaler 200/6

[b] The submission incorrectly calculated the therapeutic equivalent dose of salbutamol as 49 mcg/day instead of 78.4 mcg/day.

6.46 The submission incorrectly used DMPQ and private prices in the cost-minimisation analysis. During the evaluation, using AEMP, applying correct therapeutic equivalent dose of salbutamol and without any private prices, the cost per patient per year for Symbicort was $6.79 more than ICS+SABA in mild asthma. The PSCR argued that the submission correctly applied the DPMQ in the cost-minimisation analysis based on the Guidelines for preparing submissions to the PBAC, Version 5.0, and that when DPMQ is used, and when the equi-effective dose of salbutamol is used, Symbicort ($71.14/year) is less costly than ICS+SABA ($79.30). 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. The pre-PBAC response continued to argue that their approach using DPMQ for the cost-minimisation analysis was appropriate and consistent with other examples. The PBAC agreed with the ESC and supported the analysis based on ex-manufacturer prices.

6.47 The ESC considered that, while the claim of non-inferiority was not robust, the cost-minimisation analysis, rather than the cost-utility analysis, was the most appropriate economic analysis for this submission. The ESC noted that the cost-minimisation analysis should aim to achieve a cost that is no greater than the cost of the comparator ICS+SABA. With this focus in mind, the ESC considered 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 (e.g. patients may have an inhaler at home and one in their bag or car), which may affect the results of the cost-minimisation analysis.

The PBAC noted the proposed Symbicort product information states that patients should be advised to always have 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 ESC that patients are likely to have more than one Symbicort inhaler in use at a time and considered that this would affect the results of the cost-minimisation analysis presented.

Cost-utility analysis

6.48 The submission presented a cost-utility analysis in the form of a trial-based expected cohort analysis to compare Symbicort to SABA. The submission's modelling approach did not appear to be reflective of the chronic nature of the disease. Longer time horizons are required to sufficiently demonstrate all related risks and benefits in such conditions.[3]

6.49 The trial population was not reflective of the PBS population in which Symbicort would replace SABA and thus was of limited value in determining the incremental cost effectiveness of Symbicort over SABA. The appropriate trial population should be all patients with mild asthma; however, the patients in the trials did not include treatment-naïve patients to allow the evaluation of treatment initiation with Symbicort.

6.50 Based on exacerbations alone, Symbicort appeared to be dominant, mainly driven by reduced moderate and severe exacerbations resulting in reduced hospitalisations and emergency department visits.

6.51 No price advantage for Symbicort was claimed based on the cost-utility analysis and hence it may be considered supplementary.

6.52 The PSCR argued that the cost-utility analysis comparing Symbicort to SABA should be considered relevant as the trial population was appropriate. The ESC noted the results of the analysis but agreed with the evaluation that they were of limited value, due to the inappropriate (more severe) trial population for the comparison.

[3] Campbell J, Spackman D, Sullivan SJA. Health economics of asthma: assessing the value of asthma interventions. 2008;63(12):1581-92.

Drug cost/patient: $49.49 per year

6.53 Applying the AEMP and excluding non-PBS prices for the comparators, the annual cost per patient was $49.49 for Symbicort.

6.54 Table 13 presents the differences between costs and doses in trial compared to the model and financial estimates.

Table 13: Drug cost per patient for proposed and comparator drugs

	Symbicort Trial dose	Symbicort Cost min AEMP	Proposed drug Financial estimates	Budesonide/ terbutaline Trial dose	Budesonide/ salbutamol Cost min AEMP	Comparator Financial estimates
Total mean dose	83.2 mcg per day	83.2 mcg per day	83.2 mcg per day	201/196 mcg per day	201/49 mcg per day	Multiple drugs
Cost/patient/year		$49.49[a]	$44.64[b]/$49.31[c]		$42.70[a]	Multiple drugs

Source: Table 3.5, p60 of the submission and Compiled during evaluation
[a]Compiled during evaluation
[b]DPMQ for Symbicort Turbuhaler 200/6
[c]DPMQ for Symbicort Rapihaler 100/3

Estimated PBS usage & financial implications

6.55 This submission was considered by DUSC.

6.56 To estimate the financial impact of listing Symbicort on the PBS/RPBS, the submission presented an epidemiological approach to estimate the number of patients uncontrolled on SABA as needed who would be eligible for Symbicort and a market share approach to determine the eligible population who would switch to Symbicort from ICS+SABA.

6.57 The submission used Australian population and asthma prevalence data along with a population based cross-sectional survey (Reddel 2017) to determine the number of patients uncontrolled on SABA as needed who presented for a healthcare visit and had the opportunity to be offered Symbicort. An uptake rate of [redacted]% in year 1, [redacted]% in year 2, [redacted]% in year 3 and [redacted]% in years 4 to 6 was then applied.

6.58 The submission used 10% PBS sample data for five low dose ICS products and applied assumptions regarding switching rates to determine the number of eligible ICS+SABA patients.

6.59 Table 14 provides the estimated use and financial implications of PBS listing Symbicort.

Table 14: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of Symbicort[b]						
Cost to the PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Copayments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS less copayments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications for ICS						
Cost-offsets to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net financial implications[b]						
Net cost to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Government health budgets saving excl. GP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net impact on Government health budgets	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 4.2.2 – 4.4.3, p76-84 of the submission, and calculated during evaluation using the correct co-payment (see note b below)
ICS = inhaled corticosteroid; PBS = pharmaceutical benefits scheme; RPBS = repatriation pharmaceutical benefits scheme
[a] 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
[b] 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 evaluation to 74.42% and 25.58% (J27 and K27 in Sheet 2b excel workbook)

6.60 At year 6, the estimated number of patients was 100,000-200,000 and the estimated cost of Symbicort to the PBS/RPBS would be less than $10 million. The estimated financial implications for the PBS/RPBS and the government health budget of listing Symbicort were uncertain as:

- The uptake rate for patients uncontrolled on SABA may be underestimated given that patients who are uncontrolled and present with the opportunity to switch to Symbicort may be more inclined to take up an as needed therapy rather than a daily ICS therapy. The uptake rate for patients uncontrolled on SABA may also be an underestimate in light of the high use of ICS+LABA FDC therapy in comparison to the use of ICS.
- A larger patient population would be eligible for Symbicort under the GINA (2019) framework. This was addressed in the scenario analysis.
- The switch rates for ICS+SABA to Symbicort might be lower than estimated as those patents compliant with daily ICS would be unlikely to switch to Symbicort. Alternatively, the switch rates may be higher for some patients for whom the

convenience of using one inhaler (Symbicort) when needed rather than two separate inhalers (ICS daily and SABA as needed) is preferable.

- The cost-savings were largely uncertain as the reduced healthcare resource utilisation applied, mainly due to fewer exacerbations in patients treated with Symbicort compared to SABA, were sourced from SYGMA 1. The SYGMA 1 trial only included patients uncontrolled on SABA as needed or controlled on ICS+SABA and hence it does not include all patients eligible for Step 2 treatment according to the NAC (2019) guidelines. The cost saving is therefore likely to be an overestimate, as the proposed PBS population is likely to include patients with less frequent asthma symptoms.

6.61 DUSC considered the estimates presented in the submission to be underestimated. The main issues are:

- 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 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 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.

6.62 The pre-PBAC response argued that the number of packs estimated was appropriate as the average number of Symbicort packs per patient per year (1.58) was based on the utilisation of ICS in the Symbicort arm of SYGMA 2 (i.e. mean 83.2 mcg/day) and

the number of inhalations per Symbicort pack (i.e. 160 mcg per inhalation and there are 120 inhalations per pack). The PBAC disagreed with the pre-PBAC response that the average number of packs per patient per year proposed was appropriate. 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.

6.63 The PBAC also considered that the risk of inappropriate use of Symbicort as needed on a seasonal basis in the management of upper respiratory tract infections in patients without asthma was high.

Estimated PBS usage and financial implications considering the updated GINA (2019) framework

6.64 A scenario analysis was conducted during the evaluation based on the updated GINA (2019) framework, which no longer recommend SABA as needed in step 1 treatment, is presented in Table 15. The assumptions used in the scenario analysis were:

- all patients with mild asthma who are on SABA as needed would be eligible for Symbicort;
- 100% of eligible patients will have the opportunity to use Symbicort (i.e. visit to GP or emergency room) since it was the only preferred step 1 treatment;
- 80% of eligible patients will be treated with Symbicort since it is the preferred controller listed in step 1 and one of the two preferred controllers in step 2; and
- no change for the substitution of Symbicort for ICS+SABA since ICS+SABA remain as one of the preferred controller for step 2 patients.

Table 15: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of Symbicort						
Net total cost to the PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS less copayments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications for ICS						
Cost-offsets to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net financial implications						
Net cost to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Compiled during the evaluation
ICS = inhaled corticosteroid; PBS = pharmaceutical benefits scheme; RPBS = repatriation pharmaceutical benefits scheme
[a] Average number of units per year based on the average dose (83.2 mcg/day) in SYGMA 2 trial and inhalations per Symbicort pack

6.65 Based on the recommendations from the GINA (2019) framework, a substantially increased number of patients would be likely to take up Symbicort, i.e. over 200,000

in Year 1, increasing to over 200,000 in Year 6. The estimated cost of Symbicort to the PBS/RPBS was $30 - $60 million in Year 1, increasing to $30-$60 million in Year 6. The PSCR argued that the scenario analysis was not applicable as the financial modelling in the submission was based on patients eligible for step 2 of the NAC guidelines. DUSC considered that the scenario analysis was likely an overestimate, particularly in Year 1, as 100% of people will not present to a GP or emergency room, and 80% uptake in Year 1 is unlikely.

Quality Use of Medicines

6.66 A number of quality use of medicines initiatives for patients and healthcare professionals were proposed by the sponsor to ensure the appropriate use of Symbicort. The initiatives included the continuous update of the NAC guidelines and the provision of education for patients/cares and healthcare professionals regarding the risk of SABA over-reliance and the need for ICS due to the inflammatory nature of asthma.

6.67 The ESC considered that use of Symbicort, as proposed by the submission, may be particularly beneficial in the adolescent and pregnant women populations, potentially better and/or safer than SABA alone. However, the ESC noted that use of Symbicort in children less than 12 years is not in accordance with the proposed restriction and, as such, advised that provider education will be required in order to prevent inappropriate use in this population. The PBAC considered that provider education will also be required to prevent inappropriate use of Symbicort as needed in allergen-induced or exercise-induced bronchoconstriction and also in patients without asthma who have an upper respiratory tract infection.

6.68 DUSC questioned whether the intention is to replace SABA with Symbicort for emergency use, such as in hospitals and doctor's bags. The pre-PBAC response stated that, at this stage, the sponsor has no intention to seek an indication in these settings.

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

7 PBAC Outcome

7.1 The PBAC did not recommend an extension of the current 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. This recommendation was primarily based on concerns regarding the claim of non-inferior clinical effectiveness compared with ICS+SABA, the approach taken in the cost-minimisation analysis, and that the financial consequences of listing were uncertain.

7.2 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.

7.3 The PBAC noted that the PSCR confirmed that the intent of the proposed restriction was to allow Symbicort to be reimbursed as an alternative to ICS+SABA in patients requiring step 2 of the NAC (2019) guidelines. The PBAC considered the proposed place in therapy appropriate and consistent with the proposed TGA indication. However, the PBAC also agreed with the ESC that, as the guidelines recommend that most patients with mild asthma initiate treatment with ICS+SABA (i.e. step 2) rather than a SABA (i.e. step 1), the proposed PBS population is broader than the submission PICO and the clinical trial evidence presented as the latter do not include treatment-naïve patients.

7.4 The PBAC considered that ICS+SABA was the appropriate main comparator considering the proposed place in therapy.

7.5 The PBAC agreed with the ESC that the comparison with SABA was not appropriate as the intention is that Symbicort be used at step 2 of the NAC guidelines, where an ICS is indicated. The PBAC noted the recent update of the GINA (2019) framework with SABA as needed treatment no longer recommended at step 1 and as such, patients at any disease severity would likely be initiated on Symbicort. The PBAC agreed with the ESC that there was no clinical evidence presented to support the use of Symbicort in this population or to conduct an economic evaluation in this line of therapy.

7.6 The PBAC noted the key clinical trial evidence supporting the proposed listing and the two different primary outcomes for the two main studies, that is, well controlled asthma weeks (WCAW) for SYGMA 1 and rate of severe exacerbations for SYGMA 2. 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). In addition, the PBAC was concerned regarding the submissions 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 < 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. 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.

7.7 Due to concerns with the results reported for severe asthma exacerbations and WCAW, the PBAC considered that the claim of non-inferior comparative effectiveness versus ICS+SABA was uncertain.

7.8 The PBAC noted that the asthma exacerbation and symptom control outcomes

reported for Symbicort were achieved with a lower level of ICS use than reported in the ICS+SABA arms of the SYGMA 1 and SYGMA 2 trials. In addition, the PBAC noted that there were no significant safety differences reported between Symbicort and ICS+SABA. The PBAC considered the claim of comparable safety versus ICS+SABA as needed was reasonable.

7.9 In considering the applicability of the trial data, the PBAC agreed with the ESC that the Australian population for which Symbicort is proposed to be used is likely to be a population with milder asthma compared to the populations included in the SYGMA trials as the Australian setting would include treatment-naïve patients. In addition, the PBAC considered that the lower rate of smoking observed in the trial populations may potentially impact the treatment effect of Symbicort as Australian patients may be more likely to have more frequent exacerbations due to smoking status. However, overall the PBAC considered the trial data applicable to step 2 of the NAC guidelines where most people with mild asthma will initiate therapy.

7.10 The PBAC agreed with the ESC that, while the claim of non-inferior comparative effectiveness was not robust, 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. 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.

7.11 The PBAC considered that the cost-utility analysis versus SABA was not informative for this submission due to the inappropriate (more severe) trial population for the comparison.

7.12 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 product information states that patients should be advised to always have 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 a Risk Sharing Arrangement may be required for Symbicort to address the risk of use beyond the proposed population and to address the uncertain financial estimates.

7.13 The PBAC considered that a number of quality use of medicines issues were evident for the proposed listing including the potential for inappropriate use in patients aged < 12 years, in exercise-induced bronchoconstriction or in patients with an upper respiratory tract infection without asthma. The PBAC also considered the mixed consumer comments from major asthma related organisations highlighted confusion as to how the proposed listing would work in clinical practice. The PBAC noted that a number of quality use of medicines initiatives for patients and healthcare professionals were proposed by the sponsor but considered that more information was required to allay concerns regarding the potential for inappropriate use of Symbicort as needed in clinical practice.

7.14 The PBAC recommended that, before making a resubmission, the sponsor consult with asthma related organisations such as the National Asthma Council, 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 a Risk Sharing Arrangement which includes a cap may be the most appropriate way forward in addressing the financial uncertainty.

7.15 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

8 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.

9 Sponsor's Comment

The sponsor had no comment.