

**6.15 BECLOMETASONE WITH FORMOTEROL,
Pressurised inhalation containing beclometasone
dipropionate 100 micrograms and formoterol
fumarate dihydrate 6 micrograms per dose, 120 dose,
Fostair[®],
Chiesi Australia Pty Ltd.**

1 Purpose of submission

- 1.1 The Category 2 submission requested an Authority Required (Streamlined) listing of Fostair[®], a fixed-dose combination (FDC) of beclometasone (BEC) 100 µg, an inhaled corticosteroid (ICS), plus formoterol (FOR) 6 µg, a long-acting beta agonist (LABA) delivered via a pressurised metered dose inhaler (MDI) as maintenance and reliever treatment (MART) for asthma.
- 1.2 If listed, BEC/FOR 100/6 will be the second ICS/LABA FDC drug combination to be available on the PBS as MART for asthma.
- 1.3 Listing was requested on the basis of a cost-minimisation approach vs the FDC of budesonide (BUD) 200 µg plus FOR 6 µg (BUD/FOR 200/6) dry powder inhaler (DPI).

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

Component	Description
Population	<u>Patient who experiences 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.^a</u>
Intervention	BEC/FOR100/6 (beclometasone dipropionate 100 µg per actuation + formoterol fumarate 6 µg per actuation), 120 actuations. For maintenance therapy, one or two inhalations twice daily (maximum daily dose of 4 inhalations). For maintenance and reliever therapy (MART), patients take daily maintenance dose of BEC/FOR 100/6 and in addition take BEC/FOR 100/6 as needed in response to asthma symptoms (maximum daily dose of 8 inhalations).
Comparator	<u>Symbicort Turbuhaler 200/6 x 1 pack and Rilast TURBUHALER 200/6 x 1 pack (PBS Item 8625Y); DuoResp Spiromax 200/6 x 1 pack and BiResp Spiromax 200/6 x 1 pack (PBS Item 11273H); and Symbicort Rapihaler 100/3 x 2 packs and Rilast RAPIHALER 100/3 x 2 packs (PBS Item 10015D). Symbicort (BUD/FOR 200/6) is used as representative of the 3 comparators, as clinical trial evidence for the indirect treatment comparison for BEC/FOR (100/6) is based on Symbicort (BUD/FOR 200/6) studies.^b</u>
Outcomes	<u>Primary outcome:^c</u> <ul style="list-style-type: none"> • Time to first severe exacerbation <u>Secondary outcomes:^d</u> <ul style="list-style-type: none"> • Severe exacerbation rate • Rate of Exacerbations resulting in ER visits or hospitalisation • Change from baseline in FEV1 • Change from baseline in ACQ symptom score • Change from baseline in reliever use
Clinical claim	<u>BEC/FOR 100/6 MART (100 µg extrafine beclometasone / 6µg formoterol as MART) is non-inferior in terms of efficacy and safety compared to BUD/FOR 200/6 MART (200µg budesonide / 6 µg formoterol as MART) for the treatment of asthma.^e</u>

Source: Table 1, p2 of the submission. Clinical claim statement from Section 2.8 (p72 of the submission). Underline denotes changes compared with Table 1, beclometasone dipropionate with formoterol fumarate dihydrate, PSD, July 2020 PBAC meeting.

ACQ= asthma control questionnaire; BEC= beclometasone dipropionate; BUD= budesonide; ER= emergency room; FEV1= forced expiratory volume in 1 second; FOR= formoterol fumarate; ICS = inhaled corticosteroids; LABA = long-acting beta2 agonist; MART= maintenance and reliever therapy; PBS= Pharmaceutical Benefits Scheme; PEF = peak expiratory flow; µg= microgram.

^a The population in the July 2020 submission was 'Patients with asthma where use of a combination product (ICS+LABA) is appropriate, namely patients not adequately controlled with ICS and 'as needed' inhaled rapid-acting beta2 agonist, or patients already adequately controlled on both ICS and LABAs'.

^b The comparators in the July 2020 submission were (i) individual components (BEC and FOR) administered concomitantly via separate inhalers, (ii) Fluticasone propionate (FP)/salmeterol (SAL) metered dose inhaler (125/25 mcg per actuation) or dry powder inhaler (250/50 mcg per actuation), (iii) Budesonide (BUD)/FOR metered dose inhaler (200/6 mcg per actuation) or dry powder (200/6 mcg per actuation).

^c The primary outcomes in the July 2020 submission were morning pre-dose PEF and change from baseline FEV1 at 5 min post-dose.

^d The secondary outcomes (patient relevant) in the July 2020 submission were asthma control, day and night clinical symptoms and asthma exacerbations.

^e The clinical claim in the July 2020 submission was 'BEC/FOR is non-inferior in terms of efficacy and safety to all the proposed comparators in patients not adequately controlled with ICS and 'as needed' inhaled rapid-acting beta2 agonist, or patients already adequately controlled on both ICS and LABAs'.

2 Background

Registration status

2.1 BEC/FOR 100/6 was approved by the TGA on the 12 February 2020 for the following indication: "adults (18 years and older) in the treatment of asthma where the use of a combination product (inhaled corticosteroid and long-acting beta2-agonist) is appropriate:

- patients not adequately controlled with inhaled corticosteroids (ICS) and 'as needed' inhaled rapid-acting beta2-agonist, or
- patients already adequately controlled on both ICS and long-acting beta2-agonists (LABA).”

2.2 The TGA indication for BEC/FOR 100/6 does not specifically indicate use as MART for asthma, but the wording is broad, and the approved prescribing information provides dosing recommendations as MART for asthma.

Previous PBAC consideration

2.3 The PBAC did not recommend BEC/FOR 100/6 as MART in July 2020 due to concerns that the data presented were not adequate to support listing for this indication and the potential for quality use of medicine issues (Paragraph 7.2, beclometasone dipropionate with formoterol fumarate dihydrate, Public Summary Document (PSD), July 2020 PBAC meeting).

2.4 A summary of the previous consideration by the PBAC in July 2020 relating to MART and how the submission addressed them is presented in Table 2.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the submission addressed it
Inappropriate comparator	The PBAC considered that a more appropriate comparator would have been the formulations of BUD/FOR currently PBS listed for MART and noted that no data were presented for this comparison (Paragraph 7.10, July 2020 PSD).	Addressed. The submission nominated BUD/FOR 200/6 as the comparator, and included the relevant BUD/FOR (SAKURA, SMILE, STAY and Patel 2013) trials in the submission. The submission used as needed SABA as the common comparator for the indirect treatment comparison.

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Component	Matter of concern	How the submission addressed it
TGA indication	The PBAC noted that BEC/FOR is not TGA registered for anti-inflammatory reliever therapy. The PBAC considered that if, like certain formulations of BUD/FOR, BEC/FOR was PBS listed for MART the potential for confusion and inappropriate use as an anti-inflammatory reliever therapy in mild asthma was high (Paragraph 7.9, July 2020 PSD).	Partially addressed. The TGA approved BEC/FOR 100/6 on the 12 February 2020 for: <ul style="list-style-type: none"> • Maintenance therapy and • MART. The NAC also now recommends BEC/FOR 100/6 as MART. ¹ However, TGA approved BUD/FOR 200/6 for: <ul style="list-style-type: none"> • Anti-inflammatory reliever therapy (patients with mild disease); • Maintenance therapy; and • Anti-inflammatory reliever plus maintenance therapy. These differences could lead to confusion and inappropriate use of BEC/FOR 100/6 as an anti-inflammatory reliever therapy in mild asthma (if BEC/FOR 100/6 is PBS listed for MART).
Exclusion of relevant trials	Papi 2013 compared BEC/FOR as MART versus BEC/FOR plus as needed SABA. The submission inappropriately excluded the trial because the circumstances of use differed from the maintenance trials (Paragraphs 6.4 & 7.2, July 2020 PSD).	Addressed adequately by including the relevant trials in the submission. The submission presented results from the Papi (2013) trial (BEC/FOR 100/6 as MART vs BEC/FOR + as needed SABA). The submission included the relevant BUD/FOR trials (SAKURA, SMILE, STAY and Patel 2013) in the indirect treatment comparisons.
Comparative efficacy	In Papi 2013, patients receiving both maintenance and as needed BEC/FOR (i.e., MART) were significantly less likely to have a severe exacerbation than those taking BEC/FOR plus as needed salbutamol (12% vs 18%, HR=0.64, 95% CI 0.49-0.82). The submission did not present any evidence to inform the comparable efficacy between BEC/FOR as MART versus other ICS/LABA FDC products available on the PBS for MART (Paragraphs 6.14 & 7.2, July 2020 PSD).	Addressed adequately by providing a comparison with the efficacy of BUD/FOR as MART. See above.
Comparative safety	In Papi 2013, the number of drug-related AEs was higher for patients treated with BEC/FOR as MART compared to patients treated with BEC/FOR as maintenance therapy plus as needed salbutamol (4.4% vs 2.2%). The submission did not present any evidence to inform the comparative safety between as needed BEC/FOR versus other ICS/LABA FDC products available on the PBS for MART (i.e., BUD/FOR) (Paragraphs 6.16 & 7.2, July 2020 PSD).	Addressed adequately by providing additional safety data. The submission assessed the safety of BEC/FOR 100/6 as MART with BEC/FOR 100/6 + as needed SABA (CSR-0042). Additionally, safety comparisons were made between BEC/FOR 100/6 as MART and BUD/FOR as MART, based on the SAKURA, SMILE, STAY, and Patel (2013) trials.

¹ National Asthma Council Australia, (2023), Australian Asthma Handbook. National Asthma Council Australia, Melbourne. Website. Available from: <http://www.astmahandbook.org.au> [Accessed 13th December 2023]

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Component	Matter of concern	How the submission addressed it
Clinical claim	The submission did not make a clinical claim for use in MART (Paragraph 6.23, July 2020 PSD).	Addressed adequately by making a clinical claim for MART. The submission claimed that BEC/FOR 100/6 as MART is non-inferior in terms of efficacy and safety compared to BUD/FOR 200/6 as MART for the treatment of asthma.
Quality use of medicines	Given the sponsor is requesting listing for only one strength of BEC/FOR inhaler, patients that require lower or higher doses of ICS would need to switch to an alternative ICS/LABA FDC. This need to switch ICS/LABA FDCs for dose changes has the potential to increase patient confusion and inappropriate use. (Paragraphs 6.43 & 7.2, July 2020 PSD).	Not adequately addressed. The submission claimed that BEC/FOR 100/6 and BUD/FOR co-exist as MART options internationally and concern regarding quality use of medicines was unwarranted. The submission referenced working closely with the NAC, the inclusion of BEC/FOR 100/6 as MART in the TGA PI, and the GINA guidelines.

Source: Table 7, p12 of the submission; Paragraphs 6.0-7.10, beclometasone dipropionate with formoterol fumarate dihydrate, PSD, July 2020 PBAC meeting.

BEC = beclometasone dipropionate; BUD = budesonide; FDC = fixed-dose combination; FOR = formoterol fumarate; GINA = Global Initiative for Asthma; ICS = inhaled corticosteroids; LABA = long-acting beta2 agonist; MART = maintenance and reliever therapy; NAC = National Asthma Council; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PI = Product information; PSD = public summary document; TGA = Therapeutic Goods Administration.

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

3 Requested listing

Name, Restriction, Manner of administration and form	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
BECLOMETASONE DIPROPIONATE AND FORMOTEROL FUMARATE					
beclometasone dipropionate 100 microgram/actuation + formoterol fumarate dihydrate 6 microgram/actuation inhalation, 120 actuations	\$37.82 published price \$█ proposed price	1	1	5	Fostair

Category / Program: Section 85 General Schedule
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"/>
Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED)
Condition: Asthma
Indication: Asthma
Treatment Phase: N/A
Clinical criteria: Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids; 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.
Treatment criteria: N/A
Population criteria: Patient must be aged 18 years or older.
Administrative Advice: 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). Patient must not be on a concomitant single agent 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. This product is not PBS-subsidised for use as 'anti-inflammatory reliever' therapy for mild asthma.

ICS = inhaled corticosteroid; LABA = long-acting beta2 agonist; N/A = not applicable; NAC = National Asthma Council; PBS= Pharmaceutical Benefits Scheme.

- 3.1 The submission did not propose any special pricing arrangements.
- 3.2 The current AEMP for BEC/FOR 100/6 for the asthma maintenance indication is \$23.09. The proposed AEMP for BEC/FOR 100/6 for the asthma MART indication was slightly lower at \$|. The submission requested a weighted AEMP for BEC/FOR 100/6 of \$| (DPMQ \$|), based on a weighted price between that derived for MART and the existing asthma maintenance indication. The submission assumed utilisation for the current asthma maintenance indication and MART to be a 90:10 ratio. No justification for this assumption was provided.
- 3.3 There are currently no ICS/LABA FDCs on the PBS containing the combination of BEC/FOR as MART for asthma. Both of the individual components of the BEC/FOR FDC

are available on the PBS for the treatment of asthma. BEC 100 µg is available as 2 MDI formulations (Qvar 100 MDI (PBS item 8407L) has an unrestricted listing; Qvar 100 Autohaler MDI (PBS item 8409M)). FOR 6 µg is available as 2 dry powder inhaler (DPI) formulations with restricted listings (Oxis Turbuhaler DPI (PBS item 8239P); Foradile DPI (PBS item 8136F)).

- 3.4 The proposed maximum quantity and repeats were consistent with other ICS/LABA FDC products used as MART for asthma.
- 3.5 The proposed clinical and population criteria were similar to the existing PBS restrictions for the comparator (BUD/FOR 200/6). However, the following difference was noted:
- The proposed listing for BEC/FOR 100/6 was for adults (18 years and over), whereas BUD/FOR 200/6 is PBS listed for adults and adolescents (12 years and older). The BEC/FOR 100/6 trial (CSR-0042) included participants who were 18 years or older.
 - The proposed restriction for BEC/FOR 100/6 excluded anti-inflammatory reliver therapy for mild asthma (Step 2 of the algorithm). There are several BUD/FOR (200/6 and 100/3) PBS listings as anti-inflammatory reliver therapy for mild asthma (Step 2 of the algorithm) (PBS items 12029D, 12041R, and 12042T).
- 3.6 The Australian Asthma Handbook recommended BEC/FOR 100/6 as MART solely at Step 3, while BUD/FOR 200/6 can be used at both Step 3 and Step 4². In contrast, GINA guidelines recommended both BUD/FOR 200/6 and BEC/FOR 100/6 as MART in Steps 3 and 4³. The proposed restriction for BEC/FOR 100/6 as MART did not specify which step(s) are appropriate. Differences between BEC/FOR 100/6 and BUD/FOR (200/6 and 100/3) as MART in terms of the PBS restriction and Australian clinical management algorithm may cause confusion and inappropriate use of BEC/FOR 100/6.
- 3.7 Overall, the requested restriction was consistent with the TGA indication, the clinical evidence presented, the cost-minimisation approach presented and the estimation of use in clinical practice.

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

² National Asthma Council Australia (2019). Australian Asthma Handbook: Management Adults (Version 2.0) Available from: <https://www.astmahandbook.org.au/static/files/Australian-Asthma-Handbook-v2.0-Management-%E2%80%93-Adults.pdf>. [Accessed 4th December 2023].

³ Global Initiative for Asthma (GINA), (2023), Global strategy for asthma management and prevention. Available from https://ginasthma.org/wp-content/uploads/2023/07/GINA-2023-Full-report-23_07_06-WMS.pdf. [Accessed 17th November 2023].

4 Population and disease

- 4.1 Asthma is a chronic inflammatory disease of the airways that is defined clinically as the presence of airflow limitation and respiratory symptoms (e.g. wheeze, shortness of breath, cough, chest tightness) that vary over time. The primary goal of asthma pharmacotherapy is to reduce underlying inflammation and promote bronchodilation.
- 4.2 Pharmacological management involves a stepwise approach. In the current Australian guidelines, patients who experience exacerbations or uncontrolled asthma despite ICS maintenance treatment would initiate low dose ICS/LABA (Step 3), progressing to medium and high dose ICS/LABA if asthma remains uncontrolled (Step 4). In addition to regular maintenance treatment to prevent symptoms, patients use as needed rapid acting bronchodilators, such as short-acting beta2 agonist (SABA), for relief of symptoms. Under the MART regimen, instead of using a SABA, patients use a low dose ICS/LABA FDC (containing FOR) for both maintenance treatment and as needed for relief of symptoms.
- 4.3 BEC/FOR 100/6 is a low dose ICS/LABA FDC delivered via a hydrofluoroalkane pressurised MDI, with a total of 120 actuations. It contains an extrafine particle size formulation of BEC, which produces a more potent effect than non-extrafine formulations of BEC. The PBAC has accepted that a dose of 100 µg extrafine BEC is equivalent to 250 µg non-extrafine BEC. All BEC inhalers available on the PBS are extrafine formulations (Qvar[®] 50 or 100 and Qvar[®] Autohaler[®] 50 or 100); non-extrafine inhalers were delisted in 2002.
- 4.4 The submission proposed that BEC/FOR 100/6 would be an alternative ICS/LABA as MART (in Step 3 of the treatment algorithm) for patients who experience regular asthma symptoms while receiving treatments with ICS and LABA. ICS/LABA as MART is currently available as an FDC (e.g., BUD/FOR).
- 4.5 The submission stated that the stepped approach to adjusting asthma medication suggested that a PBS listing for MART, BEC/FOR 100/6 could be used at Step 3 and/or Step 4, along with BUD/FOR 200/6, and that this would provide another alternative MART option for patients. The Australian Asthma Handbook included BEC/FOR as MART at Step 3 of the treatment algorithm only, compared to both Step 3 and Step 4 for BUD/FOR (200/6 and 100/3) (see Paragraph 3.6). Further, the TGA approved BEC/FOR 100/6 as maintenance therapy and MART in response to asthma symptoms, but not as anti-inflammatory reliever therapy for patients with mild asthma (see Paragraph 3.5).
- 4.6 The Australian Asthma Handbook and Global Initiative for Asthma guidelines consider 200 µg of BEC per day to be a low dose ICS, while 400 µg daily is categorised as a medium dose (at the higher end of the range).

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

5 Comparator

- 5.1 The submission nominated BUD/FOR (200/6 µg) (PBS item 8625Y, originator brand Symbicort Turbuhaler DPI (200/6 x 1 pack of 120 actuations); and follow-on generic Rilast Turbuhaler DPI (200/6 x 1 pack of 120 actuations)) as the main comparator. The submission argued that BUD/FOR DPI 200/6 has a restriction as MART for asthma and provided the same equi-effective dose of ICS/LABA per day as BEC/FOR 100/6. In July 2020, the PBAC accepted that BUD/FOR 200/6 was the appropriate comparator for BEC/FOR 100/6 as MART (Paragraph 7.10, beclometasone dipropionate with formoterol fumarate dihydrate, PSD, July 2020 PBAC meeting). The evaluation considered the nominated comparator was appropriate and that the submission provided adequate justification for the nominated comparator.
- 5.2 The submission also nominated the following PBS-listed brands of BUD/FOR as comparators since they have a restriction as MART for asthma and provide the same equi-effective dose of ICS/LABA per day as BEC/FOR 100/6:
- DuoResp Spiromax DPI (200/6 x 1 pack of 120 actuations) and BiResp Spiromax DPI (200/6 x 1 pack of 120 actuations) (PBS item 11273H), and
 - Symbicort Rapihaler MDI (100/3 x 2 packs each of 120 actuations) and Rilast RAPIHALER MDI (100/3 x 2 packs each of 120 actuations) (PBS item 10015D).
- 5.3 The submission stated that BEC and FOR were not appropriate comparators because the individual components do not have a MART indication on the PBS. However, the submission included the individual components, BEC and FOR, at the same daily doses as recommended for BEC/FOR 100/6 as MART in the cost-minimisation approach, consistent with the PBAC Guidelines 2016 v5.0 for fixed-dose comparisons. The evaluation considered this was appropriate.
- 5.4 BUD/FOR 100/3 MDI (PBS item 10015D) was PBS listed on the basis of cost-minimisation to BUD/FOR 200/6 DPI (PBS item 8625Y), assuming 2 actuations of the MDI are equivalent to one actuation of the DPI formulation. That is, the Therapeutic Relativities assume the same duration of treatment by accounting for the fact that one script of BUD/FOR MDI provides twice as many actuations compared to BUD/FOR DPI (240 vs 120 actuations).

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 two organisations via the Consumer Comments facility on the PBS website. The comments from Asthma Australia stated

that BEC/FOR 100/6 as MART has been demonstrated to be effective and would increase consumer choice of ICS medicine and devices for MART, which may improve asthma control. Asthma Australia also indicated that up to 90% of people with asthma do not use their inhaler correctly. Asthma Australia suggested that sufficient resources and education be provided to healthcare professionals and consumers to ensure optimal understanding of this product and appropriate device technique, and to promote quality use of medicines. The National Asthma Council Australia (NAC) suggested that providing another option for MART in the treatment of adults with moderate to severe asthma would benefit patients, and potentially reduce the over-reliance on SABAs for symptom control.

Clinical trials

- 6.3 No head-to-head trials comparing BEC/FOR 100/6 as MART with BUD/FOR 200/6 as MART were identified.
- 6.4 The submission was based on one trial involving BEC/FOR 100/6 as MART:
 - CSR-0042 (Papi 2013) (N=1,714) [BEC/FOR 100/6 as MART vs BEC/FOR 100/6 + as needed short-acting β -agonist (SABA)].
- 6.5 The submission also presented the 4 trials involving BUD/FOR as MART:
 - SAKURA (Atienza 2013) (N=2,091) (BUD/FOR 200/6 DPI as MART vs BUD/FOR 200/6 DPI + as needed SABA).
 - SMILE (Rabe 2006) (N=3,394) (BUD/FOR 200/6 DPI as MART vs BUD/FOR 200/6 DPI + as needed SABA vs BUD/FOR 200/6 DPI + as needed LABA).
 - STAY (O'Byrne 2005) (N=2,760) (BUD/FOR 80/4.5 DPI as MART vs BUD/FOR 80/4.5 DPI + as needed SABA vs BUD + as needed SABA).
 - Patel (2013) (N=303) (BUD/FOR 200/6 MDI as MART vs BUD/FOR 200/6 MDI + as needed SABA).
- 6.6 The PBAC previously considered the CSR-0042 (Papi 2013) trial (Paragraph 6.4, beclometasone dipropionate with formoterol fumarate dihydrate, PSD, July 2020 PBAC meeting), and the SMILE and STAY trials (Paragraph 7, budesonide with formoterol fumarate dihydrate, PSD, March 2007 PBAC meeting). The PBAC has not previously considered the SAKURA and Patel (2013) trials.
- 6.7 Details of the trials presented in the submission are provided in Table 3.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
CSR-0042 NCT00861926/ EUCTR2008-004671-22- IT	A 48-week, multicentre, multinational, randomised, double blind, 2-arm parallel group study, comparing the efficacy of FOSTER® for maintenance and reliever versus fixed-dose FOSTER® for maintenance + salbutamol as reliever in asthmatics ≥18 years of age. Papi, A., et al. Beclometasone–formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomised controlled trial.	CSR, July 2011 <i>Lancet Respir Med</i> 2013; 1(1): 23-31.
SAKURA NCT00839800 EUCTR2008-006869-86- HU	A Comparison of Symbicort® SMART (160/4.5µg) and Symbicort® Turbuhaler 160/4.5 µg, Plus Terbutaline Turbuhaler 0.4 mg as Needed, for Treatment of Asthma - a 12-month, Randomised, Double-blind, Parallel Group, Active-controlled, Multinational Phase III Study in Asthmatic Patients From 16 Years. Atienza T, Aquino T, Fernández M, Boonsawat W, Kawai M, Kudo T, Ekelund J, Ivanov S, Carlsson LG. Budesonide/formoterol maintenance and reliever therapy via Turbuhaler versus fixed-dose budesonide/formoterol plus terbutaline in patients with asthma: phase III study results. Atienza T., Aquino T., Fernandez M., Boonsawat W., Kawai M., Ekelund J., Ivanov S., Carlsson L.-G. Budesonide/Formoterol Maintenance And Reliever Therapy Via Turbuhaler® Vs Fixed-Dose Budesonide/Formoterol Plus Terbutaline In Patients With Asthma: Phase III Study Results.	Date not provided. <i>Respirology</i> 2013;18(2): 354-63 <i>American Journal of Respiratory and Critical Care Medicine</i> 2012;185:A3950
SMILE	Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study.	<i>Lancet</i> 2006; 26;368 (9537):744-53
STAY	Efficacy and safety of budesonide/formoterol (Symbicort) Turbuhaler® as Single Therapy in patients with mild-moderate asthma. Comparison with Symbicort Turbuhaler and Pulmicort® Turbuhaler as maintenance therapy, both complemented with Bricanyl® Turbuhaler (STAY). O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, Ekström T, Bateman ED. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma.	Date not provided <i>Am J Respir Crit Care Med</i> 2005 15;171(2):129-36
Patel 2013 ACTRN12610000515099	A randomised, controlled trial to investigate the "real-life" use of the Vannair "SMART" regime in adult asthma (the SMART study) Patel M, Pilcher J, Pritchard A, Perrin K, Travers J, Shaw D, Holt S, Harwood M, Black P, Weatherall M, Beasley R; SMART Study Group. Efficacy and safety of maintenance and reliever combination budesonide-formoterol inhaler in patients with asthma at risk of severe exacerbations: a randomised controlled trial.	Date not provided <i>Lancet Respir Med</i> 2013;1(1):32-42

Source: Table 13, p27 of the submission.

6.8 The key features of the indirect evidence are summarised in Table 4.

Table 4: Key features of the included trials

Trial	N	Design / duration	ICS/LABA component	SABA component	Bias	Patient population	Key Outcomes
BEC/FOR 100/6 as MART vs BEC/FOR 100/6 maintenance + as needed SABA							
CSR-0042 Papi (2013)	1,714	P3, MC, R, DB 2wk run-in 48 weeks	BEC/FOR 100/6 MDI	Salbutamol	Low	Asthma for 6 months, aged ≥18y, FEV1 ≥60%, one or more severe exacerbations in the past year, treated with ICS or ICS/LABA	Time to first severe asthma exacerbation
BUD/FOR as MART vs BUD/FOR maintenance + as needed SABA							
SAKURA	2,091 ^a	P3, MC, R, DB 2wk run-in 12 months	BUD/FOR 200/6 DPI	Terbutaline	Low	Asthma patients, aged ≥16y, one severe exacerbation in the 12 months prior to study entry), receiving maintenance ICS.	Time to first severe asthma exacerbation
SMILE	3,394 ^a	MC, R, DB 2wk run-in 12 months	BUD/FOR ^b 200/6 DPI	Terbutaline	Low	Asthma for 6 months aged ≥12y, had more than one severe asthma exacerbation in the 12 months, used ICS for at least 3 months.	Time to first severe asthma exacerbation
STAY	2,760 ^a	MC, R, DB 2wk run-in 12 months	BUD/FOR 80/4.5 DPI	Terbutaline	Low	Asthma for 6 months, aged 4y-80y, FEV1 ≥60%, one or more severe exacerbations in the past year, treated with ICS in the last 12 months.	Time to first severe asthma exacerbation
Patel (2013)	303	R, OL 24 wk No run-in period	BUD/FOR 200/6 MDI	Salbutamol	Medium	Asthma patients, aged 16–65y, at least one asthma exacerbation in the last year, receiving maintenance ICS.	One episode of high use (high-use episode) of β agonist
Pooled (primary analysis)	2156 ^c	Included relevant treatment arms of SAKURA and SMILE trials					Time to first severe asthma exacerbation
Pooled (sensitivity analysis)	3232	Included relevant treatment arms of SAKUA, SMILE, STAY and Patel (2013) trials					Time to first severe asthma exacerbation

Source: Table 19, pp39-40 of the submission; pp28-32 of the submission; and relevant trial publications. Risk of bias judgement added during the evaluation.

BEC = beclometasone; BUD = budesonide; DB = double blind; DPI = dry powder inhaler; FOR = formoterol; FEV1 = forced expiratory volume in the first second of expiration; FP = fluticasone propionate; FVC = forced vital capacity; ICS = inhaled corticosteroid; LABA = long-acting β2-agonist; MC = multicentre; OL = open-label; P3 = phase three; PEF = peak expiratory flow; MDI = pressurised metered dose inhaler; R = randomised; SAL = salbutamol; tx = treatment; wk = week; y = year.

Note: The Patel (2013) trial used the time to first severe asthma as the secondary outcome. The Patel (2013) trial administered 2 inhalations twice daily. Hence, the total daily ICS/LABA maintenance dose was 800/24. The SAKURA and SMILE trials used one inhalation twice daily (ICS/LABA maintenance dose 400/12 per day). The STAY trial used 80/4.5 µg twice daily.

^a includes randomised participants from treatment arms not relevant to the submission.

^b The SMILE trial indicated that delivered dose was BEC/FOR 160/4.5 µg. SABA= terbutaline 0.5 mg (metered dose; delivered dose 0.4 mg). Information on delivered dose was not available from the relevant studies of the SAKURA, SMILE and Patel (2013) trials.

^c Calculated based on values presented for the MART treatment arms in Table 19 of the submission.

6.9 The number of participants in the SMILE and STAY trials that were randomised into treatment arms relevant to this submission were 2,451 and 2,254, respectively. In addition, 1,137 participants in the SMILE trial were randomised into a BUD/FOR 200/6 DPI + as needed LABA (formoterol) arm and 925 participants in the STAY trial were randomised into a BUD 320 µg twice a day + terbutaline 0.4 µg as needed (BUD

- + as needed SABA). These treatment arms were not relevant as the comparator arm relevant for this submission was ICS/LABA + as needed SABA.
- 6.10 The doses of BUD in the ICS/LABA treatment arms were 80 µg in the STAY trial, rather than 160µg (delivered dose) in the SMILE and SAKURA trials. However, the ICS/LABA doses were the same in each treatment arm [BUD/FOR 80/4.5 µg DPI twice a day + 80/4.5 µg as MART vs BUD/FOR 80/4.5 µg DPI twice a day + as needed SABA (terbutaline 0.4 mg)], enabling a comparison of ICS/LABA as MART vs ICS/LABA + as needed SABA in the common treatment arm of an indirect comparison. The evaluation considered this was reasonable. Furthermore, the STAY trial was only included in the sensitivity analysis.
- 6.11 The Patel et al. (2013) trial evaluated a high daily maintenance dose of BUD/FOR MDI (800µg/24µg daily), which was twice as high as the daily maintenance dose in the SMILE and SAKURA trials (400µg/12µg daily). However, the BUD/FOR 200/6 MDI doses were the same in both arms of the Patel (2013) trial, allowing for a comparison of ICS/LABA as MART vs ICS/LABA + as needed SABA (salbutamol) in the common treatment arm of an indirect comparison. The evaluation considered this was reasonable. Furthermore, the Patel (2013) trial was only included in the sensitivity analysis.
- 6.12 The overall risk of bias was assessed during the evaluation to be low in the CSR-0042, SAKURA, SMILE and STAY trials. The PBAC previously considered that the CSR-0042 (Papi 2013) trial had a low risk of bias (Paragraph 6.5, beclometasone dipropionate with formoterol fumarate dihydrate, PSD, July 2020 PBAC meeting).
- 6.13 The Patel (2013) trial was sensitive to several potential biases due to its open-label design (participants, investigators, and statisticians were not blinded to the treatment allocation), single hospital and smaller sample size. Therefore, the risk of bias for the Patel (2013) trial was considered to be medium.
- 6.14 Table 5 represents the factors that may cause heterogeneity in the comparative treatment effects in the CSR-0042, SAKURA and SMILE trials.

Table 5: Factors that may cause heterogeneity in the comparative treatment effects in the CSR-0042, SAKURA and SMILE trials

Category	Factor	Variation
Eligibility criteria	Asthma exacerbation history	Participants enrolled in the CSR-0042 trial had a history of at least one severe exacerbation in the preceding 12 months, while those in the SAKURA trial had at least one asthma exacerbation within the previous 12 months.
	Age	The SAKURA and SMILE trials included participants aged ≥ 16 and ≥ 12 years, respectively. In contrast, the CSR-0042 trial included participants who were 18 years old or older.
	ICS/LABA treatment prior to screening	The CSR-0042 trial included participants who previously used ≥ 1000 $\mu\text{g/day}$ BEC (non-extrafine) equivalents in ICS alone or BEC (or equivalents in ICS) ≥ 500 $\mu\text{g/day}$ plus LABA. None of the other trials used this criterion.
	Systematic corticosteroids use	The CSR-0042 and SMILE trials excluded participants who used systematic corticosteroids within one month of study entry. The SAKURA, STAY, and Patel (2013) trials did not have this exclusion criterion.
Participant characteristics	Baseline ICS dose	The mean baseline BEC dose was between 1,128 μg and 1,139 μg of BEC (non-extrafine) per day in the CSR-0042 trial. Based on the accepted therapeutic relativities, this is approximately equivalent to between 451 μg and 456 μg of BEC extrafine. Based on the equi-effective dose of BEC extrafine and BUD, this is equivalent to between 902 μg and 911 μg of BUD. The mean baseline BUD dose varied between 1020-1025 μg per day in the SAKURA trial, 751-758 μg per day in the SMILE trial, 598-691 μg per day in the STAY trial, and 805-813 μg per day in the Patel (2013) trial.
	Baseline LABA use	Compared to the SAKURA and SMILE trials, the CSR-0042 trial had a higher proportion of participants with prior LABA use (60% vs 80%).
Treatment	Maximum inhalations per day	The CSR-0042 trial allowed a maximum of up to 6 extra inhalations per day. In contrast, the SAKURA, SMILE and STAY trials allowed up to 8 extra inhalations per day.
	Reliever	The CSR-0042 trial used salbutamol as a SABA reliever. The SAKURA and SMILE trials used terbutaline.
Outcome measured	FEV1	In the CSR-0042 trial, the endpoint was assessed at Week 48 (end of the trial). However, in the SAKURA and SMILE trials, this endpoint was reported as an average value of available data during clinic visits.
	ACQ scores	In the CSR-0042 trial, the ACQ-7 scoring was conducted by the investigator. In the SMILE trial, participants completed the ACQ-5 scoring during clinic visits.
	Reliever use	The CSR-0042 trial established the baseline as the mean of the last 7 measurable values during the run-in period (before the randomisation visit). In the SAKURA and SMILE trials, the baseline was established as the average of the last 10 days prior to randomisation. In the CSR-0042 trial, the endpoint was assessed as the mean values from 7 days prior to Week 48 (end of treatment). In the SAKURA trial, the endpoint was determined using means across all post-randomisation visits.

Source: compiled during the evaluation based on Tables 16, 17, 19 and 20, pp34-37 and 39-45 of the submission; pp51-57 of the submission. ACQ = asthma control questionnaire; FEV1 = forced expiratory volume in one second; ICS = inhaled corticosteroid; LABA = long-acting β_2 -agonist; SABA = short-acting β -agonist.

6.15 The PBAC previously noted similar transitivity issues in terms of disease severity, asthma exacerbations, and ICS/LABA combinations, dosages and dose frequencies in their consideration of fluticasone furoate with umeclidinium and vilanterol, and beclometasone with formoterol and glycopyrronium as treatment for severe asthma (Paragraphs 6.12 and 7.5, fluticasone furoate with umeclidinium and vilanterol, PSD, November 2021 PBAC meeting; Paragraphs 6.10, 6.11, and 7.4, beclometasone with formoterol and glycopyrronium, PSD, March 2022 PBAC meeting).

- 6.16 The characteristics of the participants included in the CSR-0042 trial were consistent with the proposed listing. Nevertheless, the participants enrolled in the CSR-0042 trial were likely to be different than the population proposed for the PBS listing. Inclusion criteria for the trial specified a previous ICS dosage ≥ 1000 $\mu\text{g}/\text{day}$ BEC (non-extrafine) equivalents in ICS alone (20% of the participants), or ≥ 500 $\mu\text{g}/\text{day}$ with LABA utilisation (80% of the participants). The Global Initiative for Asthma guidelines recommend BEC (MDI, non-extrafine) doses greater than 500-1000 μg as a medium dose. The submission proposed BEC/FOR 100/6 be used as low dose ICS/LABA in Step 3 of the Australian clinical management algorithm. Therefore, it is probable that the CSR-0042 trial enrolled participants with more severe asthma than those proposed for inclusion in the PBS listing.
- 6.17 The submission used the outcomes time to first severe asthma exacerbation and rate of severe asthma exacerbations to support the clinical efficacy claim. These outcomes were the primary outcomes in the CSR-0042, SAKURA, SMILE, and STAY trials. The PBAC previously considered the outcome (time to first severe asthma exacerbation) in the BUD/FOR 200/6 as MART submission (Paragraph 8, budesonide with eformoterol efumarate dihydrate, PSD, March 2007 PBAC meeting).
- 6.18 The included trials used changes from baseline in forced expiratory volume in one second (FEV1) as a secondary outcome. The PBAC previously agreed that using FEV1 as the primary outcome for the purposes of assessing non-inferiority was reasonable for the maintenance therapy of severe asthma (Paragraph 7.5, fluticasone furoate with umeclidinium and vilanterol, PSD, November 2021 PBAC meeting).
- 6.19 The submission did not nominate a minimum clinically important difference (MCID) for the primary outcome time to severe asthma exacerbations. The evaluation considered this was reasonable. The PBAC has not previously indicated an MCID for severe asthma exacerbation. Furthermore, no validated MCID in the reduction of severe asthma exacerbations is available.
- 6.20 The proposed MICDs for the CSR-0042 trial include:
- 0.1L change in FEV1 from baseline.
 - 0.5 point improvement in total asthma control questionnaire (7-item) (ACQ-7) scores.
 - 0.81 reduction in reliever puffs per day.
 - 18.79 L/minute for changes in peak expiratory flow (PEF).
- 6.21 The evaluation considered these MCIDs were appropriate. The PBAC previously considered the MCID for FEV1 in July 2015 (paragraph 7.5, tiotropium bromide, PSD, July 2015 PBAC meeting). Previous studies have validated the MCIDs presented for changes from baseline in total ACQ-7 scores, reliever use and PEF. Nonetheless, the submission did not make a clinical claim based on the change from baseline in FEV1, total ACQ-7 scores, reliever use/day and PEF.

Comparative effectiveness

6.22 Key results of the CSR-0042 (Papi 2013) trial are presented in Table 6.

Table 6: Key efficacy outcomes reported in the CSR-0042 trial

	BEC/FOR 100/6 as MART	BEC/FOR 100/6 + as needed SABA	Comparative results (95%CI)	p-value
Primary outcome (Hazard ratio comparison)				
Time to first severe asthma exacerbation	-	-	HR = 0.64 (0.49;0.82)	< 0.001 0.0005^a
Primary outcome (Rate ratio comparison)				
Severe asthma exacerbations [Number of events (rate per 100 participants'/year)]	130 (14.76)	196 (22.39)	RR = 0.66 (0.55;0.80)	<0.001 <0.0001^a
Secondary outcomes (Mean difference comparisons)				
Change from baseline in FEV1 (L) [Change in mean (95%CI)]	0.11 (0.08;0.14)	0.11 (0.08;0.14)	MD = 0.00 (-0.04;0.04) MD= 0.001 ^a	0.969
Change from baseline in total ACQ-7 score [Change in mean (95%CI)]	-0.48 (-0.54;-0.42)	-0.42 (-0.48;-0.37)	MD = -0.06 (-0.13;0.02)	0.137
Change from baseline in morning PEF (L/min) [Change in mean (95%CI)]	-9.07 ^b (-14.64;-3.49)	-12.75 ^b (-18.29;-7.22)	MD = 3.69 ^b (-3.51;10.88)	0.315
Change from baseline in reliever use (inhalations/24hrs) [Change in mean (95% CI)]	-0.29 (-0.38;-0.20)	-0.27 (-0.36;-0.19)	MD = -0.02 ^b (-0.13;0.10)	0.794
Change from baseline in peak evening PEF (L/min) [Change in mean (95% CI)]	-11.37 ^b (-16.79;-5.95)	-15.09 ^b (-20.56;-9.62)	MD = 3.72 ^b (-3.39;10.84)	0.305
Secondary outcome (Rate ratio comparison)				
Hospital or emergency room treatments [Number of events (rate per 100 participants/year)]	67 (6.14)	99 (9.11)	RR = 0.67 (0.54;0.84)	<0.001 0.0003^a

Source: Tables 21-28, pp48-49 & 51-56 of the submission. **Bold** indicates statistically significant results. P-values at week 48.

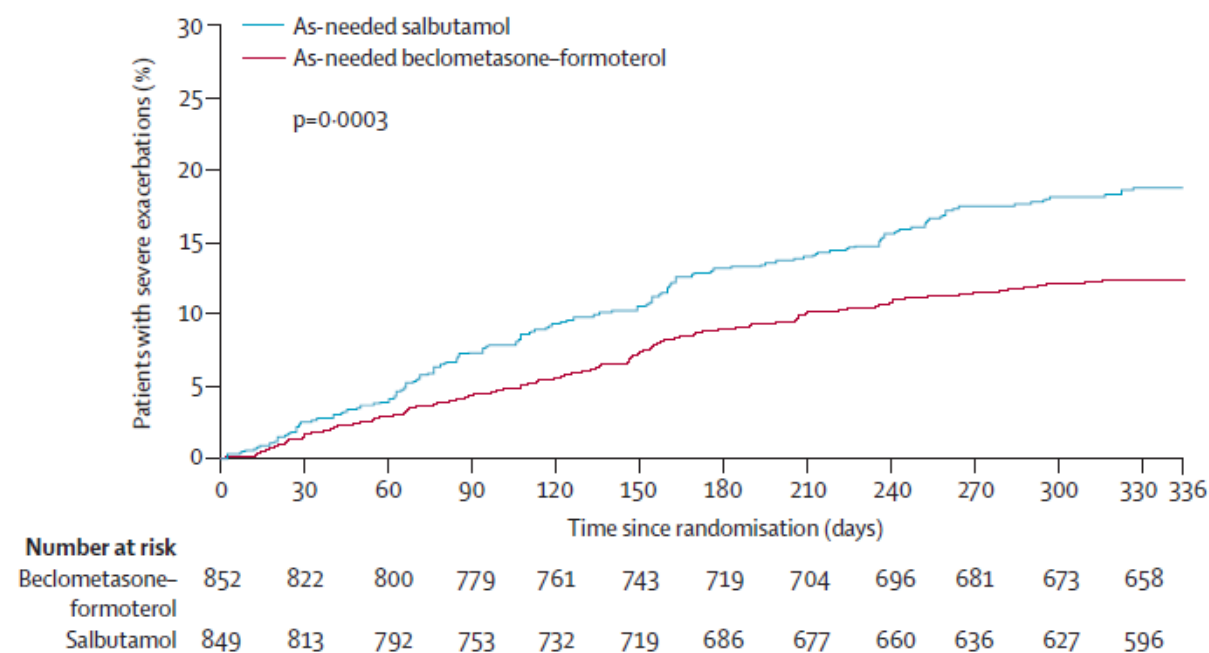
ACQ = asthma control questionnaire; BEC = beclometasone; BUD = budesonide; CI = confidence interval; FEV1 = forced expiratory volume in 1 second; FOR = formoterol; HR = Hazard Ratio; hrs = hours; MART = maintenance and reliever therapy; MD = mean difference; n = number of participants with event; N = total participants in group; NR = not reported; PEF = peak expiratory flow; RR = rate ratio; SABA = short-acting β -agonist.

^a Values were reported in the relevant studies.

^b Adjusted mean change.

6.23 Figure 1 shows the Kaplan-Meier plot for time to first severe exacerbation in the CSR-0042 trial.

Figure 1: Kaplan-Meier plot of time to first severe asthma exacerbation in the CSR-0042 trial (primary outcome)



Source: Figure 2, Papi 2013

- 6.24 In the CSR-0042 trial, using BEC/FOR 100/6 as MART significantly delayed the first asthma exacerbation (hazard ratio, HR: 0.64; 95% confidence interval (CI): 0.49, 0.82; $p = 0.0005$) and reduced the number of severe asthma exacerbations (rate ratio, RR: 0.66; 95% CI: 0.55, 0.80; $p < 0.0001$) compared to using BEC/FOR 100/6 + as needed SABA.
- 6.25 The improvements in FEV1 (baseline vs study endpoint) in both treatment arms were higher than the nominated MCID (0.11 L vs 0.1L). However, BEC/FOR 100/6 as MART did not show statistically significant improvement in FEV1 vs BEC/FOR 100/6 + as needed SABA at any time point ($p = 0.575$ at week 4, $p = 0.408$ at week 12, $p = 0.451$ at week 24, $p = 0.487$ at week 26 and $p = 0.969$ at week 48).
- 6.26 BEC/FOR 100/6 as MART did not show statistically significant improvement in total asthma control questionnaire-7 (ACQ-7) scores vs BEC/FOR 100/6 + as needed SABA at any time point ($p = 0.522$ at week 4, $p = 0.358$ at week 12, $p = 0.948$ at week 24, $p = 0.330$ at week 26 and $p = 0.137$ at week 48).
- 6.27 The submission stated that in the CSR-0042 trial, the change from baseline in ACQ-7 score was above the MCID of 0.5 points for BEC/FOR 100/6 as MART arm only. Since the change from baseline in total ACQ-7 score BEC/FOR 100/6 as MART was reported as 0.48 points, the MCID of 0.5 points was not reached.
- 6.28 The decrease from baseline in morning peak expiratory flow (PEF) was statistically significant in the BEC/FOR 100/6 as MART treatment arm at week 48 ($p = 0.001$), and in the BEC/FOR 100/6 + as needed SABA treatment arm from week 12 to week 48 ($p < 0.001$ at all times). BEC/FOR 100/6 as MART did not show statistically significant

- improvement in morning PEF BEC/FOR 100/6 + as needed SABA between weeks 36 ($p = 0.193$) and 48 ($p = 0.315$).
- 6.29 BEC/FOR 100/6 as MART did not show statistically significant improvement in the reduction from baseline reliever use vs BEC/FOR 100/6 + as needed SABA at any point in time ($p=0.794$ at Week 48). None of the treatment arms in the CSR-0042 trial reached the nominated MCID.
- 6.30 BEC/FOR 100/6 as MART did not show statistically significant improvement in the decrease from baseline in peak evening PEF vs BEC/FOR 100/6 + as needed SABA at week 4 ($p = 0.129$), week 24 ($p= 0.110$), week 36 ($p= 0.076$) and week 48 ($p = 0.305$). None of the differences reached the nominated MCID.
- 6.31 The rate of participants experiencing at least one asthma-related hospitalisation or emergency room visit and the overall number of such events was lower in the BEC/FOR 100/6 as MART arm vs BEC/FOR 100/6 + as needed SABA, resulting in a 33% annual reduction rate per 100 participants (HR: 0.67; 95%CI: 0.54, 0.84; $p < 0.001$).
- 6.32 Table 7 presents comparisons of the ICS/LABA as MART treatment arms vs ICS/LABA+ as needed SABA treatment arms (HR, RR and mean difference) for the included trials.

Table 7: Comparison of key outcomes presented in the BEC/FOR 100/6 and BUD/FOR trials

Trial ID	CSR-0042 (Papi 2013)	SAKURA	SMILE	STAY	Patel (2013)
Medicine comparison	BEC/FOR 100/6 as MART vs BEC/FOR 100/6 + as needed SABA	BUD/FOR 200/6 DPI as MART vs BUD/FOR 200/6 DPI + as needed SABA	BUD/FOR 200/6 as MART DPI vs BUD/FOR 200/6 DPI + as needed SABA	BUD/FOR DPI 80/4.5 as MART vs BUD/FOR 80/4.5 DPI + as needed SABA	BUD/FOR 200/6 MDI as MART vs BUD/FOR 200/6 MDI + as needed SABA
Time to first severe asthma exacerbation [HR (95% CI)]	0.64 (0.49;0.82)	0.70 (0.57;0.85)	0.55 (0.45;0.68)	0.55^a (0.44;0.67)	0.53 (0.33;0.84)
Number of severe asthma exacerbations [RR (95% CI)]	0.66 (0.55;0.80)	0.70 ^b	0.52 (0.44;0.62)	NR 0.53 ^{a,b}	NR 0.54^{b,c} (0.36;0.82)
Change from baseline in FEV1 (L) [MD (95% CI)]	0.00 (-0.04;0.04)	0.04 (0.05;0.064)	0.08 (0.05;0.10)	0.05^d (NR)	0.04 (NR)
Change from baseline in total ACQ score [MD (95% CI)]	-0.06 (-0.13;0.02)	-0.12 (-0.18;-0.07)	-0.15 (-0.21;-0.08)	NR	-0.17 ^d (NR)
Change from baseline in morning PEF [MD (95% CI)]	3.69 ^e (-3.51;10.88)	5.8 (2.1;9.5)	7.5 (4.2;10.7)	NR	NR
Number of hospital or emergency room treatments [RR (95% CI)]	0.67 (0.54;0.84)	NR 0.72^b (0.56;0.92)	0.61 (0.45;0.82)	NR	NR 0.78 ^b (0.24;2.36)
Change from baseline in reliever use [MD (95% CI)]	-0.02 (-0.13;0.1)	-0.25 (-0.36;-0.15)	-0.20 (-0.28 ; -0.11)	-0.13 (NR)	NR
Change from baseline in peak evening PEF [MD (95% CI)]	3.72 ^e (-3.39;10.84)	5.7 (2.1;9.3)	6.3 (3.1;9.5)	NR	NR

Source: Compiled during evaluation from Tables 22 and 28, pp48-56 of the submission and clinical study report of CSR-0042 trial and other relevant publications. **Bold** means statistically significant results.

BEC = beclometasone dipropionate; BUD = budesonide; CI = confidence interval; DPI = dry powder inhaler; FEV1 = forced expiratory volume at 1 second; FOR = formoterol fumarate; HR = Hazard ratio; ICS = inhaled corticosteroid; LABA = long-acting β 2-agonist; MART = maintenance and reliever therapy; MD = mean difference; NR = not reported/not available; PEF = peak expiratory flow; MDI = metered dose inhaler; RR = Rate ratio; SABA = short-acting beta-agonist.

Note: The SMILE trial indicated that the delivered dose was BEC/FOR 160/4.5 μ g. SABA= terbutaline 0.5 mg (metered dose; delivered dose 0.4 mg). Information on the delivered dose was not available from the relevant studies of the SAKURA, SMILE and Patel (2013) trials.

^a Primary endpoint definition of severe asthma exacerbation included patients with morning PEF of 70% or less of baseline on 2 consecutive days.

^b Values reported in the relevant publication (Patel et al. 2013) or values calculated during the evaluation using the following tool: https://www.medcalc.org/calc/rate_comparison.php added during the evaluation.

^c Patel (2013) used a weighted mean rate per year. A rate per 100 patients participants is not available. Relative rate values reported in the relevant publication (Patel 2013).

^d The submission indicated that the values were not reported in the paper, calculated from reported baseline and clinical outcome values (STAY) / at end of study (Patel 2013) (pp52-53 of the submission). Calculated as a simple subtraction of reported baseline values from the reported end of study values and between arm differences.

^e Adjusted mean. The CSR-0042 trial calculated the mean difference of 3.69, with as needed SABA showing a value (-12.75) compared to MART (-9.07). The CSR-0042 trial calculated the mean difference of 3.72, with as needed SABA showing a value (-15.09) compared to MART (-11.37).

- 6.33 All trials included in the submission demonstrated the superiority of ICS/LABA as MART vs comparable ICS/LABA+ as needed SABA in extending time to first severe asthma exacerbation (primary outcome for CSR-0042, SAKURA, SMILE, and STAY trials).
- 6.34 ICS/LABA as MART significantly reduced the number of severe exacerbations compared to ICS/LABA + as needed SABA across the CSR-0042, SMILE, and Patel (2013) trials.
- 6.35 BEC/FOR 100/6 as MART did not demonstrate significant improvements in FEV1, ACQ score, reliever use, and morning and evening peak PEF compared to BEC/FOR 100/6 + as needed SABA, whereas BUD/FOR as MART did achieve statistically significant benefits vs BUD/FOR + as needed SABA.

Indirect treatment comparison

- 6.36 The submission presented 2 indirect treatment comparisons. The primary indirect treatment comparison included the CSR-0042, SAKURA, and SMILE trials. The sensitivity analysis included the CSR-0042, SAKURA, SMILE, STAY and Patel (2013) trials.
- 6.37 Table 8 presents the primary indirect comparison results for time to severe exacerbation and rate of severe exacerbations with ICS/LABA as MART and ICS/LABA+ as needed SABA.

Table 8: Number of severe exacerbations with ICS/LABA as MART vs ICS/LABA+ as needed SABA and the indirect comparison results for severe exacerbations

Time to first severe exacerbation						
Trial type or estimate		Trial ID	Treatment effect (HR, 95%CI)	p-value		
BEC/FOR 100/6 as MART vs BEC/FOR 100/6 + as needed SABA trial		CSR-0042 (Papi 2013)	0.64 (0.49;0.82)	<0.001 0.0005^a		
BUD/FOR 200/6 DPI as MART vs BUD/FOR 200/6 DPI+ as needed SABA trials		SAKURA	0.70 (0.57;0.85)	0.0003		
		SMILE	0.55 (0.45;0.68)	<0.001 <0.0001^a		
BUD/FOR 200/6 DPI as MART vs BUD/FOR 200/6 DPI + as needed SABA trials		Pooled	0.62 (0.49;0.79)	NR		
Indirect estimate of effect adjusted for the common reference			1.032 ^b (0.727; 1.467)	0.859		
Rate of severe exacerbation						
Trial type or estimate	Trial ID	ICS/LABA as MART Rate	ICS/LABA + as needed SABA Rate	Treatment effect (RR, 95%CI)	p-value	
BEC/FOR 100/6 as MART vs BEC/FOR 100/6 + as needed SABA trials	CSR-0042 (Papi 2013)	14.76	22.39	0.66 (0.55;0.80)	<0.001 <0.0001^a	
BUD/FOR 200/6 DPI as MART vs BUD/FOR 200/6 DPI + as needed SABA trials	SAKURA ^b	21.4	30.7	NR 0.70^{a,b} (0.59;0.82)	NR <0.0001^a	
	SMILE	19	37	0.52 (0.44;0.62)	<0.0001	
	Pooled	40.4	67.7	0.60 (0.44;0.81)	NR	
Indirect estimate of effect adjusted for the common reference				1.100 ^d (0.765; 1.581)	0.863	

Source: Tables 21, 22, 37 and 40; pp48-49 & 67-68 of the submission; Figures 8 and 9, pp67-68 of the submission. **Bold** values indicate statistically significant results.

BEC = beclometasone dipropionate; BUD = budesonide; CI = confidence interval; CSR = clinical study report; DPI= dry powder inhaler; FAS = full analysis set; FOR = formoterol fumarate; ICS = inhaled corticosteroid; HR = hazard ratio; LABA = long-acting β 2-agonist; MART = maintenance and reliever therapy; NR = not reported; PEF = peak expiratory flow; RR = rate ratio; SABA = short-acting beta-agonist.

^a Calculated during the evaluation or reported in the relevant submission.

^b Table 37 of the submission presented the comparison BEC/FOR 100/6 to BUD/FOR 200/6 as 0.969 (95% CI: 0.682;1.376) and the comparison BUD/FOR 200/6 to BEC/FOR 100/6 as 1.032 (95% CI: 0.727;1.467). The Bucher comparison was checked during the evaluation: 1.032 (95% CI: 0.727;1.467) relates to the comparison BEC/FOR 100/6 to BUD/FOR 200/6.

^c Reported in Atienza (2013) as 0.214 per participant for MART and 0.307 per participant for BUD/FOR + as needed SABA. Hazard ratio of time to event for severe asthma exacerbation (Poisson regression) was reported in the SAKURA trial (Atienza 2013).

^d Table 40 of the submission presented the comparison BEC/FOR 100/6 to BUD/FOR 200/6 as 0.909 (95% CI: 0.632;1.307) and the comparison BUD/FOR 200/6 to BEC/FOR 100/6 as 1.100 (95% CI: 0.765;1.581). The Bucher comparison was checked during the evaluation: 1.100 (95% CI: 0.765;1.581) relates to the comparison BEC/FOR 100/6 to BUD/FOR 200/6.

6.38 The submission stated that the indirect comparison for time to severe exacerbation indicated a lack of statistical and clinical significance and was supportive of non-inferiority (HR: 1.032; 95% CI: 0.727, 1.467; p=0.859, RR: 1.100; 95% CI: 0.765, 1.581; p=0.863). These conclusions were appropriate. However, heterogeneities across the trials (CSR-0042, SAKURA and SMILE) may affect the assumption of transitivity and, thus, the indirect comparison results.

6.39 The submission stated that the findings were unchanged for the indirect comparison that included the CSR-0042, SAKURA, SMILE, STAY and Patel (2013) trials (HR: 1.085, 95% CI: 0.808, 1.457; p=0.888, RR: 1.179, 95% CI: 0.934, 1.486; p=0.919). The results of the sensitivity analysis were consistent with the primary indirect comparison.

Comparative harms

6.40 Table 9 summarises the treatment exposure and safety outcomes in the CSR-0042 trial.

Table 9: Summary of key adverse events in the CSR-0042 trial

Trial ID	BEC/FOR 100/6 as MART n (%)	BEC/FOR 100/6 + as needed SABA n (%)
CSR-0042		
N	854	854
TEAEs	379 (44.4)	380 (44.5)
TEAE With Grade 3 (severe) or Higher	56 (6.6)	79 (9.3)
Serious TEAEs	32 (3.7)	41 (4.8)
Drug related TEAEs	38 (4.4)	19 (2.2)
Serious drug related TEAEs	0	1 (0.1)
TEAEs leading to study treatment discontinuation	10 (1.2)	21 (2.5)
TEAEs leading to death ^b	1 (0.1)	2 (0.2)

Source: Tables 31 and 33, p62-63 of the submission.

BEC = beclometasone dipropionate; FOR = formoterol fumarate; MART = Maintenance and Reliever Therapy; SABA = Short-Acting β -Agonist; TEAE = Treatment Emergent Adverse Event.

6.41 Previously, the PBAC noted that the number of drug-related adverse events was higher for participants treated with BEC/FOR 100/6 as MART compared to participants treated with BEC/FOR 100/6 + as needed SABA arm (4.4% vs 2.2%) (Paragraph 7.10, beclometasone dipropionate with formoterol fumarate dihydrate, PSD, July 2020 PBAC meeting).

6.42 Among the participants treated with BEC/FOR 100/6 as MART who experienced drug-related treatment-emergent adverse events (TEAEs), 11 had dysphonia, 5 had cardiac disorders, while 8 had infections and infestations. These 3 categories accounted for the majority of drug related TEAEs reported in the trial.

6.43 Table 10 compares the key adverse events of ICS/LABA as MART arms in the included trials.

Table 10: Comparison of key adverse events in the BEC/FOR 100/6 and BUD/FOR trials

Trial ID	CSR-0042	SAKURA	SMILE	STAY	Patel (2013)
Medicine comparison	BEC/FOR 100/6 as MART	BUD/FOR 200/6 DPI as MART	BUD/FOR 200/6 DPI as MART	BUD/FOR 80/4.5 DPI as MART	BUD/FOR 200/6 MDI as MART
N (SAS)	854	1,049	1,107	922	NR
TEAEs, n (%)	379 (44.4)	602 (57.4)	NR	469 (53.8) 496 (54) ^a	NR
TE serious AE, n (%)	32 (3.7)	NR (4.0)	70 (6.3)	46 (5.0)	6 (4.0) 8 (5.3) ^a
Asthma serious events, n (%)	NR	NR (0.5)	16 (1.4)	NR	NR
Related to study drugs, n (%)	38 (4.4)	NR (3.9)	NR	NR	NR
Leading to discontinuations, n (%)	10 (1.2)	11 (1.0)	NR	19 (2.1)	3 (2.0)
Death, n (%)	1 (0.1)	1 (0.1)	1 (0.1)	NR	NR

Source: Tables 31 and 32, p62 of the submission.

AE = adverse event; BEC = beclometasone dipropionate; BUD = budesonide; DPI= dry powder inhaler; FOR = formoterol fumarate; LABA = long-acting β 2-agonist; MART = maintenance and reliever therapy; MDI= metered dose inhaler; NR = not reported; SAS = safety analysis set; SABA = short-acting β -agonist; TEAE = treatment emergent adverse event.

Note: The STAY trial used 80/4.5 μ g twice daily, and the Patel (2013) trial used 200/6 μ g 2 inhalations twice daily as ICS/LABA dose.

The SMILE trial indicated that delivered dose was BEC/FOR 160/4.5 μ g. SABA= terbutaline 0.5 mg (metered dose; delivered dose 0.4 mg). Information on delivered dose was not available from the relevant studies of the SAKURA, SMILE and Patel (2013) trials.

^a Values are from relevant studies.

6.44 The submission noted that respiratory conditions and symptoms dominated the frequently reported events in the BUD/FOR trials, and event rates were balanced across the ICS/LABA as MART treatment arms. Overall, the adverse event profile of BEC/FOR 100/6 as MART in the CSR-0042 trial was similar to BUD/FOR as MART in the SAKURA, SMILE, STAY and Patel (2013) trials.

Benefits/harms

6.45 There were no expected clinically meaningful differences between BEC/FOR 100/6 and other ICS/LABA FDCs at comparable doses in terms of efficacy and safety when used as MART for asthma.

Clinical claim

6.46 The submission described BEC/FOR 100/6 as MART as:

- Non-inferior in terms of effectiveness compared with BUD/FOR 200/6 as MART, and
- Non-inferior in terms of safety compared to BUD/FOR 200/6 as MART.

6.47 The therapeutic conclusion for effectiveness presented in the submission for BEC/FOR 100/6 as MART compared to BUD/FOR as MART was uncertain because:

- No head-to-head trials were presented comparing BEC/FOR 100/6 as MART with BUD/FOR 200/6 as MART.
- The submission presented an indirect comparison using as needed SABA as the common comparator. There were differences across the trials that may affect the assumption of transitivity and, thus, the indirect comparison results:

- The BEC/FOR 100/6 trial used salbutamol as a SABA reliever, and the BUD/FOR trials (SAKURA, SMILE, STAY) used terbutaline. Evidence was not presented to justify the interchangeability of these 2 different SABA relievers. This might have impacted the findings of indirect comparison results, but the direction of the impact is uncertain.
 - There were differences in the eligibility criteria and baseline patient characteristics (e.g., age, prior ICS and LABA use, maximum inhalations per day) across the trials.
 - There were differences in the definition and/or measurement of the primary outcome (asthma exacerbations) and the secondary outcomes: change from baseline in FEV1, change from baseline in ACQ, change from baseline in morning and evening PEF, number of hospitalisations or emergency room treatments due to asthma, and change from baseline in reliever medication use.
- The submission did not nominate an MICD for the key outcome time to severe asthma exacerbations. The mean differences in change from baseline in FEV1, ACQ scores, reliever use and morning and evening PEF in the CSR-0042 trial (BEC/FOR 100/6 as MART vs BEC/FOR 100/6 + as needed SABA) were not statistically significant and did not reach the nominated MCIDs.
- 6.48 Noting these uncertainties, the evaluation considered the therapeutic conclusion of non-inferior clinical effectiveness may be reasonably supported by time to severe asthma exacerbation and rates of severe asthma exacerbation results but may not be supported by the results of the relevant secondary outcomes (e.g., change from baseline in FEV1, change from baseline in ACQ, change from baseline in morning and evening PEF). The overall safety of BEC/FOR 100/6 as MART in the CSR-0042 trial and BUD/FOR 200/6 as MART in the SAKURA and SMILE trials appeared similar.
- 6.49 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.
- 6.50 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

- 6.51 The submission presented a cost-minimisation approach (CMA) based on the claim of non-inferior efficacy and safety compared to BUD/FOR 200/6 for the treatment of asthma. A CMA was consistent with the clinical claim.
- 6.52 Table 11 presents the elements used to calculate the equi-effective doses. The July 2020 submission did not present equi-effective doses as MART for asthma (Step 3 in the clinical management algorithm); instead, it presented equi-effective doses for maintenance therapy, corresponding to medium doses of ICS (Step 4 in the clinical

management algorithm) (Paragraph 6.25, beclometasone dipropionate with formoterol fumarate dihydrate, PSD, July 2020 PBAC Meeting).

Table 11: Elements used to calculate the equi-effective dose

Treatment	PBS Item(s)	Dose/Day	Pack size	Days per pack	Days per script	Treatment regimen
BEC/FOR (100/6)	12183F	1 actuation twice daily	120	60	60	Chronic
BUD/FOR (200/6)	8625Y, 11273H	1 actuation twice daily	120	60	60	
BUD/FOR (100/3)	10015D ^a	2 actuations twice daily	2 x 120	2 x 30	60	
BEC (100) + FOR (6)	8407L + 8239P	1 actuation twice daily + 1 actuation twice daily	200 + 60	100 + 30	100 + 30	

Source: Table 45, pp74-75 of the submission.

BEC = beclometasone dipropionate; BUD = budesonide; FOR = formoterol fumarate; PBS = Pharmaceutical Benefits Scheme.

^a Maximum quantity = 2 packs.

- 6.53 The proposed equi-effective doses were consistent with the maintenance component of the CSR-0042, SAKURA, and SMILE trials. However, the proposed equi-effective doses did not consider the reliever component of BEC/FOR 100/6 and BUD/FOR 200/6 as MART in the CSR-0042, SAKURA, and SMILE trials, which differed in terms of the maximum number of daily inhalations. The proposed equi-effective doses were consistent with the approved TGA PI for the maintenance component for BEC/FOR 100/6 as MART, BUD/FOR 200/6 (Symbicort Turbuhaler DPI and BiResp Spiromax DPI) as MART, and BUD/FOR 100/3 (Symbicort Rapihaler MDI) as MART. However, the proposed equi-effective doses did not consider the reliever component of BEC/FOR 100/6, BUD/FOR DPI 200/6 or BUD/FOR MDI 100/3 as MART. The submission therefore implicitly assumed no difference in reliever component use between BEC/FOR 100/6 and BUD/FOR (200/6 or 100/3) as MART.
- 6.54 The median time on treatment and relative dose intensity were not considered in the calculations of equi-effective doses. The submission implicitly assumed 100% treatment compliance to BEC/FOR 100/6 and BUD/FOR DPI 200/6. This assumption may not be true but was consistent with the CMA presented for BEC/FOR as maintenance treatment for asthma (Paragraph 6.25, beclometasone dipropionate with formoterol fumarate dihydrate, PSD, July 2020 PBAC Meeting).
- 6.55 The submission noted that Symbicort Turbuhaler DPI (200/6) added a brand premium of \$4.00 on 1st October 2023, which is paid by the patient. The submission noted that the AEMP for Symbicort Turbuhaler DPI (200/6) remains \$22.33 so the brand premium did not alter the conclusion of lowest cost comparator calculations for BEC/FOR 100/6 as MART (submission). The evaluation considered this was reasonable.
- 6.56 The submission also presented a CMA comparing BEC/FOR 100/6 with the individual components, BEC and FOR, at the same daily doses as recommended for BEC/FOR 100/6 as MART, consistent with the PBAC guidelines for FDCs. The evaluation considered this was reasonable.
- 6.57 The submission stated that there were no differences in the prescribing and administration profiles of safety and toxicity management profiles. Therefore, the submission did not include any additional costs or cost offsets. The evaluation

considered this was reasonable since the proposed intervention and comparator are both ICS/LABA as MART for asthma.

6.58 The results of the cost-minimisation approach are presented in Table 12.

Table 12: Results of the cost-minimisation approach

Component	BEC/FOR 100/6	BUD/FOR 200/6	BUD/FOR 100/3	BEC + FOR (100 + 6)	
PBS items	12183F	8625Y, 11273H	10015D	8407L + 8239P	
Actuations per day	2	2	4	2	2
Actuations per inhaler/ pack	120	120	120	200	60
Days per pack	60	60	30	100	30
AEMP/pack	\$22.33	\$22.33	\$13.40	\$13.82	\$10.20
DPMQ	\$37.00	\$37.00	\$41.81 ^a	\$27.85	\$23.96
Packs per month (30 days)	0.5	0.5	1	0.3	1
Packs per year	6.08 6.09 ^b	6.08 6.09 ^b	12.17 12.18 ^c	3.65	12.18
Cost per year (AEMP)	\$135.93	\$135.93	\$163.15	\$50.48 + \$124.19 =\$174.66	
Difference in cost per year (AEMP)	\$0	Reference	\$27.21	\$38.73	

Source: Table 46, p78 of the submission, sheet 'Cost Minimisation = FOSTAIR_MAR' of the Section 3 workbook.

AEMP = approved ex-manufacturer price; BEC = beclometasone dipropionate; BUD = budesonide; DPMQ = dispensed price for maximum quantity; FOR = formoterol fumarate; PBS = Pharmaceutical Benefits Scheme.

^a Maximum quantity = 2 packs.

^b Sheet 'Cost Minimisation = FOSTAIR_MAR' of the Section 3 workbook shows 6.0875 (6.09 rounded to two decimal places). The cost per year calculation was verified during the evaluation using the packs per year without rounding.

^c Sheet 'Cost Minimisation = FOSTAIR_MAR' of the Section 3 workbook shows 12.1750 (12.18 rounded to two decimal places). The cost per year calculation was verified during the evaluation using the packs per year without rounding.

Drug cost/patient/year

6.59 The annual cost of BEC/FOR 100/6 as MART for asthma was \$225.24. This calculation assumed 6.0875 scripts per year at the requested DPMQ (\$37.00). The estimated cost for the comparator, BUD/FOR 200/6, was \$225.24.

6.60 The annual cost of BEC/FOR 100/6 as maintenance therapy in the July 2020 submission was \$592.19 per patient, based on the proposed DPMQ of \$48.64 and 12.18 scripts per year (Paragraph 6.23, beclometasone dipropionate with formoterol fumarate dihydrate, PSD, July 2020 PBAC Meeting).

Estimated PBS usage & financial implications

6.61 This submission was not considered by DUSC.

6.62 The submission used a market share approach to estimate the utilisation and financial impacts associated with the PBS listing of BEC/FOR 100/6 as MART for asthma. The evaluation considered this was reasonable.

6.63 Table 13 presents the key inputs used in the financial estimates.

Table 13: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Scripts in current market (ICS/LABA as MART)	763,651, based on PBS item reports for 8625Y, 11273H, 10015D (September 2022 – August 2023)	This was reasonable.
Market growth	-3.15% annually, based on PBS item reports for 8625Y, 11273H, 10015D (2012-2022). The submission estimated an average decrease using goal seek analysis.	Data presented in the Section 4 workbook shows that the average annual change for the years 2013-2022 was -2.36%.
Proportion of scripts applicable to indication	100%, assumption.	This may be overestimated. The PBS restrictions for PBS items 8625Y, 11273H, and 10015D are not exclusively for MART of asthma.
Uptake rate	1% in Years 1 and 2, 1.5% in Years 3-6, assumption	No evidence was provided to support this assumption.

Source: Tables 50 and 51, pp84-85 of the submission; pp83-84 of the submission; Sheet 'Growth_Calculation' of the Section 4 workbook. ICS = inhaled corticosteroid; LABA = long-acting β_2 -agonist; MART = maintenance and reliever therapy; PBS = Pharmaceutical Benefits Scheme.

- 6.64 The submission assumed that BEC/FOR 100/6 as MART would replace BUD/FOR as MART for asthma (PBS items 8625Y, 11273H and 10015D).
- 6.65 The submission noted that Symbicort Turbuhaler 200/6 (PBS item 8625Y) added a brand premium of \$4.00 on 1st October 2023, which is paid by the patient, such that the claimed DPMQ for the originator brand medicine is \$41.00, not \$37.00 (the cost-minimised price in Table 12). Consistent with the approach taken in the economic analysis, the higher price for Symbicort Turbuhaler (200/6) was not included in the financial estimates workbook. Given the brand premium was listed on 1st October 2023, the cost of the brand premium is incurred by the patient, and PBS statistics do not include data on the brand premium, the evaluation considered that excluding the higher price for Symbicort Turbuhaler (200/6) was reasonable.
- 6.66 Table 14 presents the estimated financial implications for the PBS listing of BEC/FOR 100/6 as MART for asthma based on the prices cost-minimised to BEC/FOR 200/6 (PBS item 8625Y, DPMQ = \$37.00).

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 scripts dispensed ^a	1	1	2	2	1	1
Estimated financial implications of BEC/FOR 100/6 as MART						
Cost to PBS/RPBS less copayments	3	3	3	3	3	3
Estimated financial implications for BUD/FOR 200/6 and BUD/FOR 100/3 as MART						
Cost to PBS/RPBS less copayments	4	4	4	4	4	4
Net financial implications						
Net cost to PBS/RPBS	4	4	4	4	4	4
Net cost to MBS	3	3	3	3	3	3
Net cost to the Australian Government	4	4	4	4	4	4
Previous submission July 2020 ^b						
Net cost to PBS/RPBS	3	3	3	3	3	3

Source: Tables 53, 55, 57, 58 and 60, pp85-89 of the submission; Table 6, Paragraph 6.36, beclometasone dipropionate with formoterol fumarate dihydrate, PBAC Minutes, July 2020 PBAC Meeting.

BEC = beclometasone dipropionate; BUD = budesonide; FOR = formoterol fumarate; MART = maintenance and reliever therapy; MBS = Medicare Benefits Schedule; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

^a Assuming 6.0875 packs per year as estimated by the submission.

^b The focus of the July 2020 submission was maintenance therapy (Step 4 of the clinical management algorithm), and different PBS item numbers were included for the market share approach.

The redacted values correspond to the following ranges:

¹ 15,000 to <10,000

² 10,000 to <20,000

³ \$0 to < \$10 million

⁴ net cost saving

- 6.67 The total cost to the PBS/RPBS of listing BEC/FOR 100/6 as MART for asthma was estimated to be net cost saving in Year 6, and a total of net cost saving in the first 6 years of listing.
- 6.68 The financial estimates predicted savings to the PBS because the DPMQ for BUD/FOR 100/3 (PBS item 10015D, DPMQ = \$41.81) was higher than the proposed DPMQ for BEC/FOR 100/6 as MART for asthma.
- 6.69 The submission identified the growth of the current MART market for asthma, the proportion of scripts applicable to the indication, and the uptake rate as potential sources of uncertainty. The proposed listing remained cost neutral in all sensitivity analyses conducted in the submission.

Quality Use of Medicines

- 6.70 The submission stated that educational materials setting out the appropriate dosing of BEC/FOR 100/6 as MART for asthma would be provided and supported by a medical team. The proposed quality use of medicines plan was limited given the number and complexity of respiratory devices currently available in Australia and the risk to consumers in terms of confusion regarding which inhalers to use when. This is particularly important given BUD/FOR 100/3 and 200/6 and BEC/FOR 100/6 all have

TGA indications for maintenance therapy and MART (Step 3 of the treatment algorithm), but only BUD/FOR 100/3 and 200/6 have TGA indications for anti-inflammatory reliever therapy for mild asthma (Step 2 of the treatment algorithm). Further, BUD/FOR (200/6 and 100/3) can be used as MART in both Step 3 and Step 4 of the Asthma Handbook algorithm whereas BEC/FOR 100/6 was only recommended as MART in Step 3 of the Asthma Handbook algorithm. BUD/FOR can also be prescribed to adults and adolescents (12 years and older) whereas BEC/FOR can only be prescribed for adults aged 18 years or older.

- 6.71 The PBAC previously considered that if, like certain formulations of BUD/FOR, BEC/FOR was PBS listed as MART for asthma the potential for confusion and inappropriate use as an anti-inflammatory reliever therapy in mild asthma was high (Paragraph 7.9, beclometasone dipropionate with formoterol fumarate dihydrate, PSD, July 2020 PBAC Meeting).
- 6.72 The pre-PBAC response noted that both the NAC and Asthma Australia both provided letters of support as part of the public consultation process. The pre-PBAC response highlighted that the sponsor has worked in close partnership with the NAC to co-create the FOSTAIR MART Asthma Action Plan which clarifies the approved age indication, MART dosing and inhaler technique. The pre-PBAC response stated that the FOSTAIR MART Asthma Action Plan is available on the NAC website and is used by the sponsor as part of its broad and proactive medical education initiatives for healthcare professionals and consumers.

Financial Management – Risk Sharing Arrangements

- 6.73 The submission did not propose a risk-sharing arrangement.
For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority Required (Streamlined) listing of the fixed dose combination (FDC) of beclometasone 100 µg with formoterol 6 µg (BEC/FOR 100/6) as maintenance and reliever treatment (MART) for asthma. The PBAC considered the indirect treatment comparison presented in the submission addressed its July 2020 concerns regarding the adequacy of the data presented for MART. The PBAC's recommendation for listing for this indication was based on, among other matters, its assessment that the cost-effectiveness of BEC/FOR would be acceptable if it were cost-minimised against the lowest price combination of PBS listed inhaled corticosteroid (ICS) with long-acting beta2 agonist (LABA) FDC therapy or combination of the individual components that are available for MART at comparable doses.
- 7.2 The PBAC noted the input from Asthma Australia and the National Asthma Council of Australia (NAC) supporting listing for this indication.
- 7.3 The PBAC recalled that in July 2020 it had advised that the formulations of budesonide with formoterol (BUD/FOR) currently PBS listed for MART would be an appropriate

comparator (Paragraph 7.10, beclometasone dipropionate with formoterol fumarate dihydrate, PSD, July 2020 PBAC meeting). The PBAC noted the comparator for this submission was consistent with its July 2020 recommendation and advised that the comparator was appropriate.

- 7.4 The PBAC recalled that the results of the CSR-0042 (Papi 2013) trial had been considered in July 2020. At that time the Committee had advised that the data presented showed that BEC/FOR 100/6 as MART significantly delayed the first asthma exacerbation compared to BEC/FOR 100/6 maintenance plus as-needed salbutamol. However, at that time no data were presented for a comparison of BEC/FOR 100/6 with formulations of BUD/FOR currently PBS listed for MART (Paragraph 7.10, beclometasone dipropionate with formoterol fumarate dihydrate, PSD, July 2020 PBAC meeting).
- 7.5 The PBAC noted that no head-to-head trials were presented in the current submission comparing BEC/FOR 100/6 as MART with BUD/FOR 200/6 as MART. However, the submission presented an indirect comparison that included the CSR-0042, SAKURA, and SMILE trials and used as needed short-acting beta2 agonist (SABA) as the common comparator. The PBAC acknowledged the factors that may cause heterogeneity in the comparative treatment effects in the CSR-0042, SAKURA and SMILE trials (see Table 5). Noting these uncertainties, the PBAC considered the claim of non-inferior clinical effectiveness was adequately supported by time to severe asthma exacerbation and rates of severe asthma exacerbation results.
- 7.6 The PBAC recalled that in July 2020 it had noted that in the CSR-0042 trial there were more treatment-related AEs in participants receiving BEC/FOR 100/6 as MART compared to those receiving BEC/FOR 100/6 plus as needed SABA (4.4% vs. 2.2%) (Paragraph 7.10, beclometasone dipropionate with formoterol fumarate dihydrate, PSD, July 2020 PBAC meeting). The PBAC noted the comparison of key adverse events of ICS/LABA as MART from the trials included in the current submission (see Table 10). Overall, the PBAC considered the adverse event profile of BEC/FOR 100/6 as MART in the CSR-0042 trial was similar to BUD/FOR as MART in the SAKURA, SMILE, STAY and Patel (2013) trials. As such, the PBAC considered that the claim of non-inferior comparative safety was reasonable.
- 7.7 The PBAC noted the submission presented a cost-minimisation approach between BEC/FOR and BUD/FOR for MART. The PBAC accepted the equi-effective doses outlined in Table 11 as the basis for the analysis. The PBAC considered the cost of BEC/FOR 100/6 should be no greater than the lowest price combination of PBS listed ICS/LABA FDC therapy or combination of the individual components that are available for MART at the comparable doses.
- 7.8 The PBAC noted the estimated PBS usage and financial implications and considered these estimates were reasonable.
- 7.9 The PBAC recalled that in July 2020 the Committee had been concerned about the potential for quality use of medicines issues. At that time the Committee had

considered that the potential for confusion and inappropriate use as an anti-inflammatory reliever therapy in mild asthma was high (Paragraphs 7.2 and 7.9, beclometasone dipropionate with formoterol fumarate dihydrate, PSD, July 2020 PBAC meeting). The PBAC noted that the Australian Asthma Handbook includes reference to BEC/FOR 100/6 as MART. The PBAC also noted the proposed restriction includes a population criteria stating the 'patient must be aged 18 years or older' and administrative advice that 'this product is not PBS-subsidised for use as 'anti-inflammatory reliever' therapy for mild asthma'. In addition, the PBAC noted the support provided by Asthma Australia and the NAC. The PBAC noted the resources and education highlighted in the pre-PBAC response and considered the Committee's previous concerns relating to this issue were adequately addressed.

- 7.10 In terms of the restriction, the PBAC noted the clinical criteria regarding MART proposed by the submission were consistent with those in the current BUD/FOR MART listings and considered that this was appropriate. The PBAC also considered it was appropriate to remove the administrative advice stating that this product is not PBS subsidised for use as 'maintenance and reliever' therapy as outlined in the recommended listing below.
- 7.11 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because BEC/FOR is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over BUD/FOR, or not expected to 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.
- 7.12 The PBAC noted that this submission is not eligible for an Independent Review, as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

- 8.1 Amend existing/recommended listing as follows:

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
BECLOMETASONE + FORMOTEROL					
beclometasone dipropionate 100 microgram/actuation + formoterol fumarate dihydrate 6 microgram/actuation inhalation, 120 actuations	12183F	1	1	5	Fostair
Restriction Summary [AMEND 11014] / Treatment of Concept: [AMEND 11057]					
Concept ID (for internal Dept. use)	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED) /amend existing code 11057				
	Indication: Asthma				
	Clinical criteria:				
	Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids; 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.				
	AND				
	Population criteria:				
	Patient must be aged 18 years or older.				
	Administrative Advice: This product is not indicated for the initiation of treatment in asthma.				
	Administrative Advice: This drug is not PBS-subsidised for the treatment of chronic obstructive pulmonary disease (COPD)				
	Administrative Advice: The patient must not be on a concomitant single agent long-acting-beta-2-agonist (LABA).				
	Administrative Advice: A LABA includes olodaterol, indacaterol, salmeterol, formoterol or vilanterol.				
	Administrative Advice: Adherence to current treatment and device (inhaler) technique should be reviewed at each clinical visit. and before "stepping up" a patient's medication regimen.				
	Administrative Advice: This product is not PBS-subsidised for use as 'anti-inflammatory reliever' therapy for mild asthma.				

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

9 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.

10 Sponsor's Comment

The sponsor had no comment.