5.02 BECLOMETASONE DIPROPRIONATE with FORMOTEROL FUMARATE DIHYDRATE, Pressurised inhalation containing beclometasone dipropionate 100 micrograms with formoterol fumarate dihydrate 6 micrograms per dose, 120 doses Fostair®, Emerge Health Pty Ltd.

1 Purpose of submission

1.1 The submission requested an Authority Required (Streamlined) listing of Fostair® metered dose inhaler (MDI), the fixed dose combination (FDC) of beclometasone dipropionate (BEC), an inhaled corticosteroid (ICS) and formoterol fumarate dihydrate (FOR), a long-acting beta2-agonist (LABA) for maintenance treatment of asthma and maintenance and reliever therapy (MART). Fostair® is available in one strength (BEC/FOR 100/6 micrograms per actuation).

1.2 If listed, BEC/FOR will be one of five ICS/LABA FDC drug combinations available on the PBS for asthma, and the second low dose ICS/LABA FDC drug combination listed for MART. Currently, all ICS/LABA FDCs available on the PBS for asthma are delivered via MDI and/or dry powder inhaler (DPI).

1.3 The basis of the requested listing was a cost-minimisation analysis versus fluticasone propionate (FP) /salmeterol (SAL) FDC. The submission also presented a cost-minimisation analysis versus the individual components of BEC and FOR administered concomitantly via separate inhaler and versus budesonide (BUD)/FOR FDC. A cost-minimisation analysis to other available ICS/LABA FDCs at the nominated equi-effective doses was conducted during the evaluation.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	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 beta$_2$ agonist, or patients already adequately controlled on both ICS and LABAs
Intervention	Fostair®, metered dose inhaler (MDI) containing beclometasone dipropionate (BEC) and formoterol fumarate (FOR), available in one strength formulation: 100/6 mcg per actuation. 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 and in addition take BEC/FOR as needed in response to asthma symptoms (maximum daily dose of 8 inhalations)
Comparator	The submission acknowledged that BEC/FOR FDC would substitute for other ICS/LABA FDCs on the PBS, at comparable doses. Clinical evidence was presented for the following relevant comparators: (i) Individual components (BEC and FOR) administered concomitantly via separate inhalers (ii) Fluticasone propionate (FP)/salmeterol (SAL) MDI (125/25 mcg per actuation) or DPI (250/50 mcg per actuation) (iii) Budesonide (BUD)/FOR MDI (200/6 mcg per actuation) or DPI (200/6 mcg per actuation)
Outcomes	Primary outcomes: • Morning pre-dose PEF • Change from baseline in FEV1 at 5 min post-dose Secondary outcomes (patient-relevant): • Asthma control • Day and night clinical symptoms • Asthma exacerbations
Clinical claim	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 beta$_2$ agonist, or patients already adequately controlled on both ICS and LABAs

Abbreviations: BEC=Beclometasone dipropionate, BUD=budesonide, DPI=dry-powder inhaler, FEV1=Forced Expiratory Volume in the first second of expiration, FOR=formoterol fumarate dehydrate, ICS=inhaled corticosteroids, LABA= long-acting β2-agonist, MDI= metered dose inhaler, PEF= peak expiratory flow
Source: Table 10, pp 4-5 of the submission

2 Background

Registration status

2.1 BEC/FOR was TGA registered on 12th Feb 2020 for the following indications:

'In adults (18 years and older) in the regular treatment of asthma where 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).

Symptomatic treatment of adults with severe COPD (FEV1 < 50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.'

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Dispensed Price for max. qty	Proprietary Name and Manufacturer	
BECLOMETASONE ~~DIPROPRIONATE~~ + FORMOTEROL ~~FUMARATE DIHYDRATE~~ *(EFORMOTEROL)* beclometasone dipropionate 100 microgram/actuation + formoterol (eformoterol) fumarate dihydrate 6 microgram/actuation inhalation, 120 actuations	NEW	1	1	5	$48.64	Fostair®	Emerge Health Pty Ltd

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☒Medical Practitioners ☒*Nurse practitioners*
Restriction Type / Method: ☒ Authority Required – Streamlined (*7970*)
Indication: Asthma
Treatment Phase: ~~Initial and continuing~~ *[blank]*
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:~~
~~Patient must not be on a concomitant single agent long-acting-beta-2-agonist (LABA)~~ ~~A LABA includes olodaterol, indacaterol, salmeterol, formoterol or vilanterol.~~
Administrative Advice: Patient must be aged 18 years or *older* ~~over~~.
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: *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.

3.2 The sponsor requested an Authority Required (Streamlined) PBS listing for BEC/FOR, for (i) maintenance treatment of asthma and (ii) MART. No special pricing arrangement was proposed.

3.3 There are currently no ICS/LABA FDCs on the PBS containing the combination of BEC/FOR, but both of the individual components are available on the PBS for the treatment of asthma in separate inhalers. BEC is available as two MDI formulations with unrestricted listings (Qvar® and Qvar® Autohaler®) and FOR is available as two DPI formulations with restricted listings (Oxis® Turbuhaler® and Foradile® Aeroliser® single dose DPI capsules).

3.4 For maintenance treatment, the recommended dose of BEC/FOR is one inhalation twice daily (STEP 3 in the treatment guidelines) or two inhalations twice daily (STEP 4

in the treatment guidelines), and the maximum daily dose for maintenance therapy is 4 inhalations. Therefore, the requested maximum quantities will provide for 60 days of treatment at STEP 3 and 30 days of treatment at STEP 4. The requested five repeats will provide for at least 6 months of treatment at the highest dose. This is consistent with the current PBS listings of alternative ICS/LABA FDC products treatment for asthma.

3.5 For MART, the recommended dose of BEC/FOR is one inhalation twice daily for maintenance and one inhalation as needed in response to symptoms, with a maximum of 8 inhalations per day. The duration of treatment provided by the requested maximum quantities and requested repeats depends on the number of doses used as needed for relief of symptoms. This is consistent with other ICS/LABA FDCs available on the PBS for MART.

3.6 The requested DPMQ was based on a cost-minimisation analysis to FP/SAL 125/25 MDI but is higher than other relevant comparators (see Economic analysis). The submission did not provide any justification to support a higher price compared to alternative therapies. Under Section 101(3B) of the National Health Act (1953), the PBAC cannot recommend listing a therapy at a price that is substantially more costly than an alternative therapy unless it is satisfied that the therapy provides, for some patients, a significant improvement in efficacy or reduction in toxicity.

3.7 The requested restriction was based on the current restrictions for ICS/LABA FDCs. The following key differences were noted:

- Patients must be aged 18 years or over for treatment with BEC/FOR, compared to 4 years for FP/SAL and 12 to 18 years for BUD/FOR depending on the brand;
- The requested restriction only included one of the two clinical criteria for MART that are included in the current restrictions for relevant ICS/LABA FDCs (e.g. Symbicort® Turbuhaler® 200/6):

  '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.'

3.8 The PBAC noted that the two clinical criteria for MART listed in paragraph 3.7 would be removed from the restriction if BEC/FOR was not listed for MART.

3.9 The PBAC noted that, despite being an ICS/LABA FDC containing FOR, BEC/FOR is not TGA approved for anti-inflammatory reliever therapy (see paragraph 4.5). The PBAC recommended the administrative note 'This product is not PBS-subsidised for use as "anti-inflammatory reliever therapy" for mild asthma' be added to the listing to reduce the risk of inappropriate use of BEC/FOR in mild asthma.

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

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 or 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 for maintenance treatment and as-needed for relief of symptoms.

4.3 BEC/FOR 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 mcg extrafine BEC is equivalent to 250 mcg 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 At a dose of one inhalation twice daily, BEC/FOR is an alternative low dose ICS/LABA FDC in STEP 3 of the treatment algorithm (which includes MART with low dose BUD/FOR). BEC/FOR may also substitute for medium dose ICS/LABA FDCs in STEP 4 of the treatment algorithm at a dose of two inhalations twice daily. The Australian Asthma Handbook and Global Initiative for Asthma (GINA) guidelines classify BEC 200 mcg per day as a 'low' dose ICS and BEC 400 mcg per day as a 'medium' dose ICS (at the upper dosage range). The equi-effective doses presented in the submission are based on medium dose BEC/FOR (i.e. BEC/FOR 100/6 two inhalations twice daily) versus medium doses of the nominated comparators, corresponding to STEP 4 in the treatment algorithm.

4.5 There was a recent change to the stepwise approach in the GINA guidelines (2019), with relevance to the current submission. The guidelines now recommend that patients can initiate asthma treatment with as-needed low dose ICS/LABA FDCs containing FOR. The product information (PI) of BEC/FOR states that "FOSTAIR is not intended for the initial management of asthma", which is consistent with the requested indication. In contrast, the PI of BUD/FOR (Symbicort® Turbuhaler® 200/6 and Symbicort® Rapihaler® 100/3 only) includes use as anti-inflammatory reliever therapy in patients with mild asthma. In November 2019, the PBAC recommended

listing of BUD/FOR (Symbicort® Turbuhaler® 200/6 and Symbicort® Rapihaler® 100/3 only) for use as an anti-inflammatory reliever therapy for the (initial) management of mild asthma in adolescents and adults (paragraph 5.1, BUD/FOR FDC, Public Summary Document, November 2019 PBAC meeting). The PBAC noted that the updated Australian Asthma Handbook to be published in July 2020 will include BUD/FOR use as anti-inflammatory reliever therapy in patients with mild asthma.[1]

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

5 Comparator

5.1 The submission appropriately acknowledged that BEC/FOR would substitute for all available ICS/LABA FDCs on the PBS at comparable doses, including both MDI and DPI formulations. For the clinical comparison, the submission nominated the following relevant comparators in the following preferred order:

- FP/SAL FDC including FP/SAL 125/25 MDI in the trial evidence, and FP/SAL 250/50 DPI in practice.
- BUD/FOR FDC including BUD/FOR 200/6 DPI in the trial evidence and BUD/FOR 200/6 MDI in practice.
- BEC + FOR administered concomitantly via separate inhalers. This comparison was informed by BEC 250 MDI (Becloforte®, non-extrafine formulation, not PBS listed) + FOR 12 DPI capsules (Foradile® Aerolizer®) in the clinical evidence, but assumed as BEC 100 (Qvar® Autohaler®) + FOR 6 (Oxis® Turbuhaler®) in the cost-minimisation analysis.

5.2 Other relevant comparisons identified by the submission included (i) FP/FOR 125/5 and (ii) fluticasone furoate (FF)/vilanterol (VIL) 100/25. The submission referred to FP/FOR and FF/VIL as 'not eligible comparators' without providing any justification, but nominated equi-effective doses via the Therapeutic Relativities and included them in the financial estimates.

5.3 The nominated comparators are appropriate, however FP/SAL as the preferred main comparator was poorly justified for the following reasons:

- The BUD/FOR inhalers are more similar to BEC/FOR than the FP/SAL inhalers because (i) they contain the same LABA component (i.e. FOR) and (ii) share the same proposed PBS listing. Unlike FP/SAL, certain formulations of BUD/FOR are listed for both maintenance treatment of asthma and MART, which is consistent with the requested listing for BEC/FOR; and

[1] National Asthma Council Australia, 2020. Preview to Australian Asthma Handbook v2.1 released. https://d8z57tiamduo7.cloudfront.net/resources/australian-asthma-handbook_-v2.1-preview-stepped-diagram_june-2020.pdf [accessed 22 July 2020].

- The submission argued that the individual component inhalers are costlier than most ICS/LABA FDCs, but this assumes the costliest combination of the individual component inhalers and only provides for 15 days of treatment. In contrast, the least costly combination of individual components that provides 30 days of treatment (the same duration as BEC/FOR at the nominated equi-effective dose) is cheaper than most of the other ICS/LABA FDCs (see Economic analysis).

The pre-PBAC response (p1) agreed with the evaluator that BUD/FOR may be the appropriate clinical and pricing comparator for BEC/FOR.

5.4 BUD/FOR 200/6 MDI may not be the relevant strength comparator at the nominated equi-effective dose, given the submission ignores the stated Therapeutic Relativities of BUD/FOR MDI (240 actuations) and BUD/FOR DPI (120 actuations). Instead, the lower strength BUD/FOR 100/3 MDI may be a more appropriate comparator given:

- It was PBS listed on the basis of cost-minimisation to BUD/FOR 200/6 DPI, assuming 2 actuations of the MDI are equivalent to 1 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).
- Unlike BUD/FOR 200/6 MDI, the lower strength BUD/FOR 100/3 MDI and BUD/FOR 200/6 DPI are PBS listed for MART.

There are cost implications depending on which strength formulation of BUD/FOR MDI is included in the cost minimisation analysis. The pre-PBAC response (p1) acknowledged that BUD/FOR 200/6 MDI may not be the relevant strength comparator as it provides treatment for 60 days.

5.5 A different sponsor is requesting listing of Atectura® Breezhaler® dry powder capsules for inhalation, which is an ICS/LABA FDC containing mometasone furoate (MF) with indacaterol (IND) at the July 2020 PBAC meeting. Hence, MF/IND FDC may be a potential near-market comparator for BEC/FOR.

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 organisations (2) via the Consumer Comments facility on the PBS website. The comments from the National Asthma Council of Australia (NAC) and Asthma Australia described a range of benefits of treatment with BEC/FOR and supported the addition of another ICS/LABA FDC product to provide greater choice for consumers and prescribers. The comments from NAC

noted that the updated Australian Asthma Handbook to be published in July 2020 will recommend BEC/FOR be used as per its TGA-approved indication (see paragraph 2.1). The NAC comments supported the listing of BEC/FOR as maintenance treatment of asthma in adults [redacted]. The NAC comments also noted the differences in the daily maximum dose of FOR between BEC/FOR and BUD/FOR regimens (daily maximum of 48 micrograms and 72 micrograms respectively).

Clinical trials

6.3 The submission was based on four head-to-head randomised trials comparing BEC/FOR as maintenance treatment to FP/SAL (Papi 2007a, Hsieh 2017), BUD/FOR (Papi 2007b), and BEC + FOR administered via separate inhalers (Huchon 2009).

6.4 The submission identified three supplementary trials (Barnes 2013, Papi 2012 and Papi 2013) but excluded them from the main clinical evidence.

- Barnes 2013 and Papi 2012 compared BEC/FOR versus FP/SAL in patients with controlled asthma on FP/SAL at baseline. The submission excluded the trials because the trial design likely favoured FP/SAL. Potential for bias is not a reasonable exclusion criteria but the exclusion of these trials was generally reasonable given the population was not directly applicable to the requested listing. Patients with controlled asthma are unlikely to switch ICS/LABA treatments, even if stepping down from a higher dose formulation. The evaluation did not include data from these trials, which nevertheless found similar results with BEC/FOR and FP/SAL.
- 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. The evaluation included data from this trial given the requested restriction includes MART and none of the other included trials provided evidence for use in MART.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
Main trials		
Papi 2007a (ICAT SE study)	Double blind, multinational, multicentre, parallel-group design clinical trial of the efficacy and tolerability of CHF 1565 (beclomethasone dipropionate 100mcg + formoterol 6mcg) MDI via HFA-134a vs. fluticasone 125mcg + salmeterol 25mcg MDI (Seretide®) in the 12-week treatment of adult patients with moderate to severe persistent asthma. Papi, A. et al. Beclomethasone/formoterol vs fluticasone/salmeterol inhaled combination in moderate to severe asthma.	CSR, May 2006 Allergy 2007; 62(10): 1182-1188.
Hsieh 2017	A double-blind, double dummy, randomized, 2-arm parallel-controlled study of Foster MDI HFA and Seretide MDI HFA in treatment of moderate to severe asthma in Taiwan. Hsieh, M.J., et al. Comparative efficacy and tolerability of beclomethasone/formoterol and fluticasone/salmeterol fixed combination in Taiwanese asthmatic patients.	CSR, April 2013 J Formos Med Assoc. 2018 Dec;117(12):1078-1085.

Trial ID	Protocol title/ Publication title	Publication citation
Papi 2007b (ICAT SY study)	Double blind, multinational, multicentre, parallel-group design clinical trial of the efficacy and tolerability of CHF 1565 (beclomethasone dipropionate 100mcg + formoterol 6mcg) MDI via HFA-134a vs. budesonide 160mcg + formoterol 4.5mcg dry powder via Turbuhaler® (Symbicort®) in the 12-week treatment of adult patients with moderate to severe persistent asthma.	CSR, May 2006
	Papi et al. Beclomethasone/formoterol versus budesonide/formoterol combination therapy in asthma.	Eur Respir J 2007; 29(4): 682-689.
Huchon 2009	Double blind, multinational, multicentre, parallel-group design clinical trial of the efficacy and tolerability of CHF 1565 (fixed association of beclomethasone dipropionate 100mcg + formoterol 6mcg) (two puffs BID) vs. beclomethasone dipropionate CFC (two puffs BID) + formoterol powder 12mcg (one capsule BID) given separately vs. beclomethasone dipropionate CFC 250mcg (two puffs BID) in a 24-week treatment of adult patients with moderate to severe persistent asthma.	CSR, September 2005
	Huchon, G., et al. Lung function and asthma control with beclomethasone and formoterol in a single inhaler	Respiratory medicine 2009; 103(1): 41-49.
Supplementary trials		
Papi 2012	Prospective randomized, open-label, multicentre, active drug controlled, parallel group design clinical trial of the efficacy and safety of beclomethasone dipropionate 400 mcg + formoterol 24 mcg MDI via HFA-134 A (FOSTERTM) vs. Fluticasone propionate 500 mcg + Salmeterol xinafoate 100 mcg (Seretide Diskus®) in the 6 months step-down treatment of adult patients with controlled asthma.	CSR, January 2011
	Papi, A. et al. Step-down from high dose fixed combination therapy in asthma patients: a randomized controlled trial.	Respiratory research 2012; 13(1): 54
Barnes 2013 (FACTO study)	A Phase IV, multinational, multicentre, double blind, double dummy, randomised, parallel group, controlled clinical study of fixed combination beclomethasone dipropionate 100mcg plus formoterol fumarate 6mcg MDI with HFA-134a propellant (CHF1535 Foster®) versus fluticasone 2050mcg plus salmeterol 50mcg DPI (Seretide® Diskus®) as maintenance treatment in controlled asthmatic patients.	CSR, December 2011
	Barnes, N. et al. Stepping-across controlled asthmatic patients to extrafine beclometasone/formoterol combination.	Pulmonary pharmacology & therapeutics 2013; 26(5): 555-561
Papi 2013	A 48-week, multicentre, multinational, randomized, 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.	CSR, July 2011
	Papi, A., et al. Beclometasone–formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomised controlled trial.	Lancet Respir Med 2013; 1(1): 23-31.

Source: Table 27, p46 of the submission.

6.5 The key features of the direct randomised trials are summarised in the table below. Patients enrolled in Huchon 2009 were also randomised to treatment with BEC alone, however data from this arm of the trial was not presented by the evaluation. Despite informing the benefit of adding FOR to BEC, BEC alone did not match one of the nominated comparators and was considered less relevant than alternative ICS/LABA comparators.

Table 3: Key features of the included evidence

Trial	N	Design / duration	Relevant comparison	Bias	Patient population	Key Outcomes
Maintenance						
Papi 2007a	228	P3,MC,R, DB 2wk run-in + 12wk tx	BEC/FOR 100/6mcg MDI vs. FP/SAL 125/25mcg MDI	Low	Moderate to severe persistent asthma (aged 18-65y) treated with ICS	Lung function (PEF, FEV1), symptom scores, exacerbations.
Hsieh 2017	253	P3, R, DB 2wk run-in + 12wk tx	BEC/FOR 100/6mcg MDI vs. FP/SAL 125/25mcg MDI	Low	Moderate to severe asthma (aged 20-65y) treated with ICS	Lung function (PEF, FEV1), asthma control test, exacerbations.
Papi 2007b	219	P3,MC,R, DB 2wk run-in + 12wk tx	BEC/FOR 100/6 mcg MDI vs. BUD/FOR 200/6mcg DPI	Low	Moderate to severe persistent asthma (aged 18-65y) treated with ICS	Lung function (PEF, FEV1), symptom scores, exacerbations.
Huchon 2009	432*	P3, MC, R, DB 2wk run-in + 24wk tx	BEC/FOR 100/6 mcg MDI vs. BEC 250mcg MDI + FOR 12mcg DPI	Low	Moderate to severe persistent asthma (aged 18-70y) treated with ICS or ICS/LABA	Lung function (PEF, FEV1), symptoms, exacerbations.
MART						
Papi 2013	1714	P3,MC,R, DB 2wk run-in + 12wk tx	BEC/FOR 100/6 mcg MDI MART vs. BEC/FOR 100/6 mcg MDI maintenance + salbutamol as reliever	Low	Asthma for 6 months, FEV1≥60%, ≥1 severe exacerbations in the past year (aged ≥18y) treated with ICS or ICS/LABA	Time to severe exacerbations

Abbreviations: BEC=beclometasone, 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, MEF50= Maximal Expiratory Flow at 50% of Vital Flow Capacity, PEF= peak expiratory flow; MDI=metered dose inhaler, SAL=salbutamol, tx=treatment, wk=week; y=year

*Comparison of BEC/FOR FDC vs. BEC + FOR via separate inhalers

Source: Table 32, p59 of the submission, and trial publications

6.6 All of the trials were phase 3, multicentre, randomised, controlled, double-blind, with a 2-week run-in period and at least 12 weeks of treatment. The dosing regimens in the maintenance trials were equivalent to those recommended for STEP 4 of the clinical management algorithm (i.e. medium dose ICS). The selection criteria were similar across the maintenance trials, including adults with moderate to severe asthma who experienced symptoms despite treatment with ICS.

6.7 The clinically relevant outcomes in asthma are differences in lung function tests, rescue medication use, symptom free days, percentage of patients with asthma exacerbations and quality of life. In past decisions, the PBAC has commonly relied on change in lung function (including change in morning peak expiratory flow, PEF; and forced expiratory volume in the first second, FEV1) for maintenance therapy, and time to first severe exacerbation for MART. These outcomes are measured across the trials but not all relevant outcomes were reported in all of the trials.

6.8 The submission nominated a non-inferiority margin for the difference in morning pre-dose PEF of -20 L/min, based on pre-specified margin in three of the maintenance trials designed to test non-inferiority on the primary morning pre-dose PEF outcome. The nominated non-inferiority margin for the difference in PEF was reasonable. The

Australian guidelines[2] refer to a 10% variation in PEF as being clinically important, which is also consistent with previous PBAC considerations for ICS/LABA FDCs.

6.9 The submission did not explicitly nominate a non-inferiority margin for any other outcome, but it was noted that Huchon 2009 also tested non-inferiority using mean difference in FEV1 at the end of the treatment period with a non-inferiority margin of - 0.20 L. The PBAC has previously accepted the non-inferiority margin of -0.15 to -0.20 L for mean difference in pre-dose FEV1 (page 4, FP/FOR FDC, PSD, July 2013 PBAC meeting; paragraph 6.4, FF/VIL FDC, PSD, March 2014 PBAC meeting) and is consistent with the MCID specified in the Australian guidelines[3].

Comparative effectiveness

6.10 Table 4 presents the results for the key lung function outcomes reported across the direct randomised trials of maintenance therapy.

[2] National Asthma Council Australia, 2019. The Australian Asthma Handbook. asthmahandbook.org.au [accessed 1 April 2020].
[3] Ibid.

Table 4: Key lung function outcomes (PEF, FEV1) across the trials – ITT population

	BEC/FOR	Comparator	Mean diff. (95% CI)
Morning pre-dose PEF in L/min at end of treatment			
BEC/FOR 100/6 2BD			
vs FP/SAL 125/25 2BD (Papi 2007a) – Wk11/12	329.6^	333.0^	-3.32(-17.92,11.28)#
vs FP/SAL 125/25 2BD (Hsieh 2017) – Wk12	398	416	p=0.2252+
vs BUD/FOR 200/6 2BD (Papi 2007b) – Wk11/12	338.3^	337.8^	0.49 (-11.97,12.95)#
vs BEC250 2BD+FOR12 BD (Huchon 2009) – Wk23/24	339.64^	332.37^	7.27 (-6.29, 20.82)†
Change in morning pre-dose PEF in L/min (95%CI) from baseline to end of treatment			
BEC/FOR 100/6 2BD			
vs FP/SAL 125/25 2BD (Papi 2007a) – Wk11/12	48.91 (38.54,59.27)	52.76 (40.20,65.10)	NR
vs FP/SAL 125/25 2BD (Hsieh 2017) – Wk12	38 (28.4, 47.5)	45 (34.4, 55.7)	p=0.8247‡
vs BUD/FOR 200/6 2BD (Papi 2007b) – Wk11/12	29.43 (19.31,39.54)	28.63 (20.39,36.87)	NR
Morning pre-dose FEV1 in L at end of treatment			
BEC/FOR 100/6 2BD			
vs FP/SAL 125/25 2BD (Papi 2007a) – Wk11/12	2.18^	2.20^	-0.02 (-0.13,0.09)#
vs BUD/FOR 200/6 2BD (Papi 2007b) – Wk11/12	2.31^	2.27^	0.04 (-0.07,0.15)#
vs BEC250 2BD+FOR12 BD (Huchon 2009) – Wk23/24	2.06^	2.02^	0.04 (-0.04,0.12)†
Change in morning pre-dose FEV1 in L (95%CI) from baseline to end of treatment			
BEC/FOR 100/6 2BD			
vs FP/SAL 125/25 2BD (Papi 2007a) – Wk11/12	0.22 (0.14,0.30)	0.25 (0.17,0.33)	NR
vs BUD/FOR 200/6 2BD (Papi 2007b) – Wk11/12	0.16 (0.07,0.25)	0.12 (0.05,0.19)	NR
Change in FEV1, from baseline pre-dose to end of treatment 5 minutes post-dose			
BEC/FOR 100/6 2BD			
vs FP/SAL 125/25 2BD (Hsieh 2017) – Wk12	0.20 (0.14,0.26)	0.14 (0.07,0.20)	p=0.5334 ‡

Abbreviations: BD=twice daily, BEC=beclometasone, BUD=budesonide, CI=confidence interval, FOR=formoterol, FEV1=forced expiratory volume in the first second of expiration, FP=fluticasone propionate, ITT=intention to treat, NR=not reported, PEF= peak expiratory flow, SAL=salmeterol

^ Least squared mean

+ difference compared using a t-test

ANCOVA model with treatment, geographic region and baseline value as covariates.

† ANCOVA model with treatment and centre as main effects, and baseline value as a covariate.

‡ ANCOVA model with treatment and centre as fixed effects, and baseline value as a covariate.

Source: Papi 2007a CSR (p48, p51), Hsieh 2017 CSR (p79), Papi 2008b CSR (p47, p50), Huchon 2009 CSR (p56, p58, pp67-68)

6.11 BEC/FOR versus BEC plus FOR

In Huchon 2009, the difference in mean morning pre-dose PEF from baseline to the end of treatment across the arms met the non-inferiority margin, where the lower 95%CI (-6.29 L/minute) was larger than the non-inferiority threshold (-20 L/minute). The trial was also designed to demonstrate non-inferiority for the difference in FEV1 at the end of treatment (controlling for baseline) across the arms. The mean difference in FEV1 reported (0.04, 95% CI -0.04, 0.12) supported the claim of non-inferiority given the lower 95%CI (-0.04 L) was larger than the non-inferiority threshold (-0.20 L).

6.12 BEC/FOR versus FP/SAL

In Papi 2007a, the difference in morning pre-dose PEF at the end of the treatment period (controlling for baseline) met the non-inferiority margin, where the unilateral 97.5%CI (-17.92 L/minute) was larger than the non-inferiority threshold (-20 L/minute). Non-inferiority was also supported by i) difference in FEV1 at the end of treatment (controlling for baseline) across the arms, where the lower 95%CI (-0.13 L)

was larger than the nominated non-inferiority threshold (-0.20 L); and ii) results from Hsieh 2017 showed similar efficacy between the comparison groups.

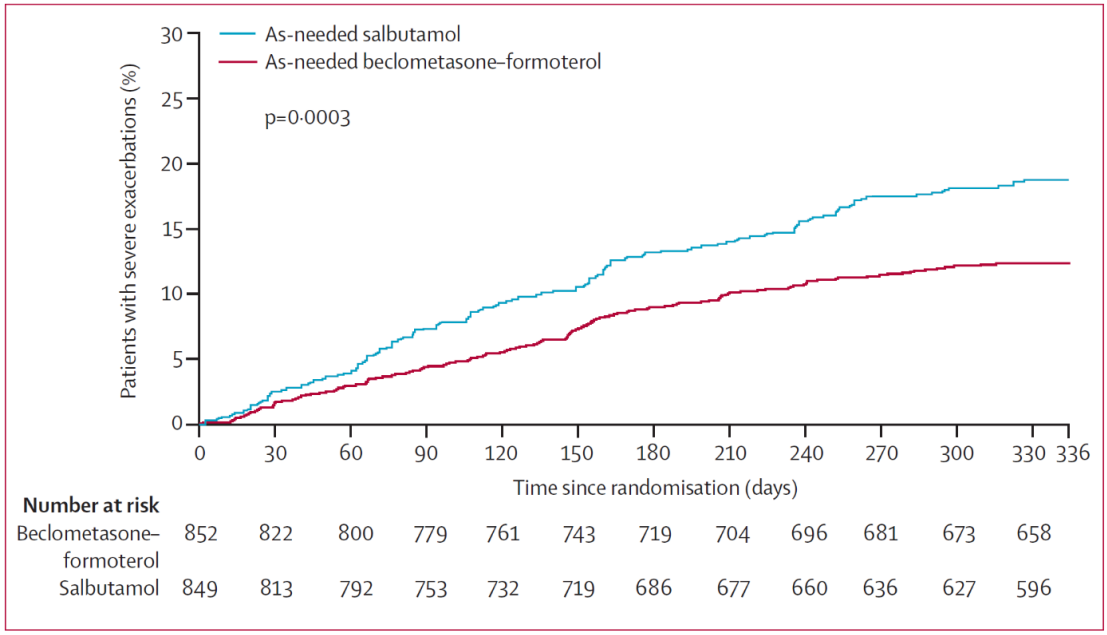
6.13 BEC/FOR versus BUD/FOR

In Papi 2007b, the difference in morning pre-dose PEF at the end of the treatment period (controlling for baseline) met the non-inferiority margin, where the unilateral 97.5%CI (-11.97 L/minute) was larger than the non-inferiority threshold (-20 L/minute). The lower 95%CI (-0.07 L) for difference in FEV1 at the end of treatment (controlling for baseline) across the arms was also larger than the nominated non-inferiority threshold (- 0.20 L).

6.14 BEC/FOR as MART versus BEC/FOR plus as needed SABA

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). Figure 1 shows the Kaplan-Meier plot of time to first severe asthma exacerbations reported in Papi 2013. 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 (i.e. BUD/FOR).

Figure 1: Kaplan-Meier plot of time to first severe asthma exacerbation (primary outcome)



Source: Papi 2013 publication

Comparative harms

6.15 Overall, there were no significant safety issues identified for BEC/FOR, with a similar proportion of adverse events (AEs) reported across all ICS/LABA FDCs in the trials. Respiratory tract infections were the most common AEs, which is consistent with the known safety profiles of the treatments.

6.16 The PBAC noted that 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. corresponding doses of BUD/FOR).

Benefits/harms

6.17 There were no expected clinically meaningful differences between BEC/FOR and other ICS/LABA FDCs at comparable doses in terms of efficacy and safety when used for the maintenance treatment of asthma.

Clinical claim

6.18 Based on the evidence presented, the submission described BEC/FOR 100/6 two inhalations twice daily as non-inferior in terms of effectiveness and safety compared to:

- BEC + FOR at comparable doses administered concomitantly via separate inhalers.
- FP/SAL 125/25 MDI two inhalations twice daily.
- BUD/FOR 200/6 DPI two inhalations twice daily.

6.19 The evidence presented in the submission supported the clinical claim of non-inferior effectiveness and safety compared to the nominated comparators, for patients requiring maintenance therapy with medium dose ICS (i.e. STEP 4 of the clinical management algorithm). At the same dosing regimen, the submission also reasonably described BEC/FOR as being non-inferior to corresponding medium doses of other ICS/LABA FDCs based on the Therapeutic Relativities (see Economic analysis).

6.20 The submission did not present any evidence to inform the effectiveness and safety of BEC/FOR at the lower recommended dose of one inhalation twice a day, for patients requiring maintenance therapy with low dose ICS (i.e. STEP 3 of the clinical management algorithm). The PBAC agreed with the evaluation that despite this, it may be reasonable to anticipate that low dose BEC/FOR would be similar to other low dose ICS/LABA FDCs based on established equi-potent doses of ICS.

6.21 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable for maintenance treatment of asthma in adults.

6.22 The PBAC considered that the claim of non-inferior comparative safety was reasonable for maintenance treatment of asthma in adults.

6.23 The PBAC noted that the submission did not make a clinical claim for use in MART. The available evidence shows that patients receiving both maintenance and as-needed BEC/FOR significantly reduced the time to first severe exacerbation compared to BEC/FOR maintenance plus as-needed salbutamol, but also resulted in more treatment-related AEs. The PBAC noted the submission did not present any evidence

comparing as-needed BEC/FOR and other ICS/LABA FDC products available on the PBS for MART (i.e. BUD/FOR inhalers).

Economic analysis

6.24 The submission presented a cost-minimisation analysis based on AEMP (per day) between BEC/FOR 100/6 and the nominated comparators. The analysis assumed no additional costs or cost-offsets.

6.25 The submission proposed the following equi-effective doses based on the trial evidence and Therapeutic Relativities, corresponding to medium doses of ICS (STEP 4 in the clinical management algorithm):

- BEC/FOR 100/6 two inhalations twice daily = 'the individual components';
- BEC/FOR 100/6 two inhalations twice daily = FP/SAL 125/25 MDI two inhalations twice daily
- BEC/FOR 100/6 two inhalations twice daily = BUD/FOR 200/6 DPI two inhalations twice daily
- BEC/FOR 100/6 two inhalations twice daily = FP/SAL 250/50 DPI one inhalation twice daily
- BEC/FOR 100/6 two inhalations twice daily = BUD/FOR 200/6 MDI two inhalations twice daily (see paragraph below)
- BEC/FOR 100/6 two inhalations twice daily = FP/FOR 125/5 two inhalations twice daily
- BEC/FOR 100/6 two inhalations twice daily = FF/VIL 100/25 one inhalation daily.

6.26 The nominated equi-effective dose for BUD/FOR 200/6 MDI may not be reasonable given one script provides for 60 days of treatment at the equi-effective dose (2x120 actuations per script), rather than 30 days of treatment for BEC/FOR (120 actuations per script). The Therapeutic Relativities determined by the PBAC provide the same duration of treatment across available products, and actually state that BUD/FOR 200/6 DPI BD = BUD/FOR 100/3 MDI 2 BD. Therefore the corresponding equi-effective dose for Fostair® is BEC/FOR 100/6 MDI 2 BD = BUD/FOR 100/3 MDI 4 BD. The pre-PBAC response (p2) acknowledged that one script of BUD/FOR 100/3 MDI includes two inhalers (total of 240 actuations) providing 30 days of treatment and hence was the relevant strength BUD/FOR MDI comparator for the calculation of equi-effective doses. The PBAC agreed with the evaluation that the equi-effective dose nominated for BUD/FOR 200/6 MDI in paragraph 6.25 was not reasonable as one script provides for 60 days of treatment.

6.27 The cost-minimisation analysis versus the individual components was based on the costliest combination of inhalers, assuming cost equivalence to BEC 100 two inhalation twice daily (Qvar® Autohaler®) plus FOR 6 DPI two inhalations twice daily (Oxis® Turbuhaler®). The Qvar® Autohaler® however, is costlier than the standard

Qvar® inhaler containing BEC 100. In addition, the Oxis® Turbuhaler® (FOR 6) used in the analysis only provides 15 days of treatment at the equi-effective dose and is costlier than both the higher strength Oxis® Turbuhaler® (FOR 12) and the Foradile® Aeroliser® (FOR 12 DPI capsules) used in the trial. The submission did not justify the choice of individual component inhalers included in the cost-minimisation analysis. The PBAC considered that an appropriate comparison of an ICS/LABA FDC with the individual components would be one that provides a similar duration of treatment (i.e. 30 days).

6.28 At the requested price (DPMQ = $48.64), BEC/FOR 100/6 MDI is cost equivalent to treatment with FP/SAL 125/25 MDI or FP/SAL 250/50 DPI, each providing 30 days of treatment.

6.29 Based on the cost-minimisation analysis presented in the submission and conducted during the evaluation at the nominated equi-effective doses, the following ICS/LABA FDCs are less costly than the requested price:

- DPMQ = $41.46 versus BUD/FOR 200/6 MDI, but this may not be the appropriate strength comparator as it provides for 60 days of treatment.
- DPMQ = $44.14 versus least costly combination of individual component inhalers, that provide at least 30 days of treatment.
- DPMQ = $44.79 versus BUD/FOR 200/6 DPI.
- DPMQ = $45.16 versus FP/FOR 125/5.

The pre-PBAC response (p1) stated that while FP/SAL has the highest ICS/LABA FDC market share, a cost-minimisation versus BUD/FOR may be more appropriate and proposed that BEC/FOR be priced against BUD/FOR 200/6 DPI.

6.30 The submission did not nominate equi-effective doses for the lower recommended dose of BEC/FOR one inhalation twice daily, or present a cost-minimisation analysis for BEC/FOR versus low dose ICS/LABA FDCs (for either maintenance treatment or MART, corresponding to STEP 3 in the clinical management algorithm). A cost-minimisation analysis between low dose BEC/FOR and other low dose ICS/FDCs is problematic because the sponsor only requested one strength formulation of BEC/FOR.

6.31 At the dose of one inhalation twice daily, BEC/FOR 100/6 provides for 60 days of low dose ICS but other low dose ICS/LABA FDCs provide 30 days of low dose ICS (e.g. FP/SAL 50/25 MDI two inhalations twice daily). A cost-minimisation between these products results in a higher price for BEC/FOR due to the longer duration of treatment, but this is not reasonable given the Therapeutic Relativities determined by the PBAC are based on products providing the same duration of treatment.

Drug cost/patient/year

6.32 The annual cost of BEC/FOR 100/6 is $592.19 per patient, based on the proposed DPMQ of $48.64 and 12.18 scripts per year.

Estimated PBS usage & financial implications

6.33 This submission was not considered by DUSC. A market share approach was used to estimate the financial implications of the proposed listing, assuming BEC/FOR would substitute for other ICS/LABA FDC products at the nominated equi-effective doses. That is, the submission only estimated the financial impact of BEC/FOR as maintenance therapy compared to medium dose ICS/LABA FDCs (STEP 4 in the clinical management algorithm).

6.34 Table 5 summarises the key inputs used in the financial estimates.

Table 5: Key inputs for financial estimates

Data	Value	Source	Comment
Market size & growth rate	Yr1: 2,000,000 to < 3,000,000 ICS/LABA scripts Symbicort® Turbuhaler® 200/6: 800,000 to < 900,000. Seretide® Accuhaler® 250/50: 400,000 to < 500,000. Symbicort® Rapihaler® 200/6: 300,000 to 400,000. Seretide® 125/25: 200,000 to < 300,000. Breo® Ellipta® 100/25: 200,000 to < 300,000. Flutiform® 125/5: 30,000 to < 40,000. Annual growth rate Yr1 to Yr6: 1.6% applied to all ICS/LABA FDCs.	Yr 1 script numbers based on 2019 value for items: 8625Y, 8431R, 10018G, 8518H, 11124L, 10007Q. Growth rate: population growth (ABS 3101.0)	Uncertain for the following reasons: i) the estimates do not include item 11273H for BUD/FOR 200/6 (DuoResp® Spiromax® brand); ii) the estimates include scripts dispensed to children and adolescents but listing is for adults; iii) the market does not include low dose ICS/LABA FDCs (STEP 3 of the clinical management algorithm).
Rate of displacement (market uptake)	Yr 1: 5% Yr 2: 10% Yr 3: 12.5% Yr 4: 14% Yr 5: 16% Yr 6: 17%	Sponsor projections	Uncertain. These rates are based on historical uptake rates in the UK and may not be directly applicable.
Rate of substitution	Symbicort® Turbuhaler® 200/6: 18% Seretide® Accuhaler® 250/50: 34% Symbicort® Rapihaler® 200/6: 12% Seretide® 125/25: 34% Breo® Ellipta® 100/25: 1% Flutiform® 125/5: 1%	Assumption.	Uncertain. No rationale was provided and there may be greater substation with BUD/FOR MDI given the similarities with BEC/FOR.
Script equivalence	Symbicort® Turbuhaler® 200/6: 12.18 Seretide® Accuhaler® 250/50: 12.18 Symbicort® Rapihaler® 200/6: 6.09 Seretide® 125/25: 12.18 Breo® Ellipta® 100/25: 12.18 Flutiform® 125/5: 12.18	Calculated as: 365.25 days per year/(actuations per pack/average actuations per day) 365.25/(120/4) =12.175 packs/patient/year Scripts / year =12.18	Reasonable.

Data	Value	Source	Comment
BEC/FOR	AEMP: $34.56 DPMQ: $48.64	Requested price	Based on the cost-minimisation analysis in section 3.
FDC Comparators DPMQ	Symbicort® Turbuhaler® 200/6 $44.79 Seretide® Accuhaler® 250/50 $48.64 Symbicort® Rapihaler® 200/6 $71.43 Seretide® 125/25 $52.64 Breo® Ellipta® 100/25 $56.51 Flutiform® 125/5 $45.16	Corresponding PBS items: 8625Y 8431R 10018G 8518H 11124L 10007Q	Inappropriate. Seretide® DPMQ (item 8518H) =$48.64; a brand premium of $4 was applied. This is inappropriate as there are other brands of FP/SAL.
Patient copayment	PBS: $20.24 RPBS: $4.89	PBS statistics (weighted average)	Reasonable

Abbreviations: FDC=fixed dose combination, MDI=metered dose inhaler
Source: Table 103, pp138-139 of the submission, Section 4 workbook.

6.35 The submission estimated the financial implications of the proposed listing based on the following approach:

- To estimate the total number of ICS/LABA FDC scripts (across the 6 nominated comparators) over the next 6 years, a constant growth rate of 1.6% was applied to the total number of scripts dispensed in the 2019 calendar year (but only from 2021 onwards). The 1.6% growth rate reflects the annual growth rate in the Australian population (which assumes a stable market).
- To estimate the number of BEC/FOR scripts that would substitute for comparator scripts, the submission correctly applied the assumed market uptake and substitution rates to the estimated market share of each comparator.
- The submission then incorrectly calculated the reduction in comparator scripts based on the projected script numbers and market uptake parameter. That is, the submission assumed the same proportional reduction in all comparator scripts based on the assumed aggregate market uptake rate for BEC/FOR (e.g. 5% in year 1, 10% in year 2, and so on).
- The net cost to the PBS/RPBS was calculated based on the corresponding DPMQs (less co-payments), but the submission inappropriately included a brand premium of $4.00 for Seretide® (FP/SAL 125/25), which was a key driver of the estimated cost-offsets.

6.36 Table 6 summarises the updated results for the financial implications, based on the corrected number of comparator scripts and the DPMQ for Seretide® (FP/SAL 125/25) without the brand premium.

Table 6: Estimated use and financial implications

	2021	2022	2023	2024	2025	2026	Total
Use and impact of proposed medicine							
Total scripts PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Cost PBS/RPBS (less co-pay)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimation of changes in use and financial impact of other FDCs							
Total scripts PBS/RPBS	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]
BUD/FOR 200/6 DPI*	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]
FP/SAL 250/50 DPI*	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]
BUD/FOR 200/6 MDI*	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]
FP/SAL 125/25 MDI*	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]
FF/VIL 100/25*	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]
FP/FOR 125/5*	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]	-[redacted]
Net Cost PBS/RPBS (less co-pay)*	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Estimated financial implications for the PBS/RPBS and the Health Budget**							
Net Cost (less co-payment)*	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Abbreviation: BUD=budesonide; FOR=formoterol; FF=fluticasone furoate; FP=fluticasone propionate; SAL=salmeterol; VI=vilanterol; MDI=metered dose inhaler; DPI=dry powder inhaler

* calculated during the evaluation from data in Section 4 workbook of the submission; the net cost to the PBS/RPBS was re-calculated by multiplying the number of substituted scripts (cells D63:P68 on '3a. Scripts – new') after adjusting the script relativity for BUD/FOR 200/6 (i.e. 0.5), by the unit costs (H180:H185 on '4c. Impact – changed (EFF)') less the co-payment (K180:L185 on '4c. Impact – changed (EFF)'), and after correcting for the unit cost of Seretide® (set H183 = $48.64 on '4c. Impact – changed (EFF)').

Source: Table 110, p145; Table 115, p149 of the submission.

**There is no predicted change to MBS item use

The redacted table shows that at Year 6 the estimated number of total scripts was 1,000,000 to < 2,000,000; and the estimated number of total scripts for the changes in use of other FDCs would reduce by 1,000,000 to < 2,000,000.

6.37 After correcting for these errors, the net cost of listing was $0 to < $10 million over the first six years of listing (compared to a cost saving presented in the submission). The proposed listing has a net cost to the PBS/RPBS because at the requested price, BEC/FOR would be equal to the second most costly ICS/LABA FDC of the nominated comparators, and would substitute for cheaper alternatives.

6.38 The financial estimates were uncertain because the analysis assumed i) all substitutions would occur between six ICS/LABA FDC products at the nominated equi-effective doses only (i.e. STEP 4 of the clinical management algorithm), ii) the estimates excluded substitution with one brand of BUD/FOR 200/6 DPI (DuoResp® Spiromax®) and iii) the estimates are not limited to an adult population. In practice under the requested restriction, BEC/FOR may also substitute for other ICS/LABA FDCs, particularly when used at a lower dose or for MART (i.e. STEP 3 in the clinical management algorithm).

6.39 The submission presented sensitivities assuming lower DPMQs of $44.79 (price equivalence to BUD/FOR 200/6 DPI) and $41.45 (price equivalence to BUD/FOR 200/6

MDI), resulting in: cost savings to the PBS/RPBS over the first six years (after correcting for the errors identified in the spreadsheet).

6.40 Given the GINA 2019 guidelines recommend patients with mild asthma commence treatment with as-needed low dose ICS/LABA FDCs containing FOR, there is potential for considerable leakage outside of the requested PBS restriction.

6.41 The PBAC noted that the financial estimates would need to be recalculated to take into account the outcome of its considerations regarding the cost-minimisation analysis. The PBAC considered that on this basis, and noting the amendments to the requested PBS restriction outlined in paragraph 3.9, the concerns raised in paragraphs 6.38 and 6.40 were adequately addressed.

Quality Use of Medicines

6.42 The sponsor will provide materials setting out the appropriate dosing with BEC/FOR, and sales representatives supported by a medical team will visit all the treating centres to educate treating physicians and nurse practitioners on the approved dosing schedules for BEC/FOR.

6.43 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.

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 (BEC) with formoterol (FOR) for the maintenance treatment of asthma only. 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 least costly combination of an inhaled corticosteroid (ICS) with a long-acting beta2 agonist (LABA) FDC or combination of the individual components (BEC + FOR) at comparable doses.

7.2 The PBAC did not recommend the listing of BEC/FOR for asthma maintenance and reliever therapy (MART) due to concerns the data presented were not adequate to support a listing for this indication and the potential for quality use of medicine issues.

7.3 In terms of the use of BEC/FOR for the maintenance treatment of asthma, the PBAC noted the input from Asthma Australia and the National Asthma Council of Australia (NAC) supporting listing for this indication.

7.4 The PBAC noted the nomination of fluticasone propionate (FP)/salmeterol (SAL), budesonide (BUD)/FOR and BEC + FOR administered concomitantly via separate inhalers as comparators and the submissions acknowledgment that BEC/FOR would

substitute for all available ICS/LABA FDCs on the PBS at comparable doses. The PBAC considered that for the maintenance treatment of asthma all ICS/LABA FDCs and the individual components (BEC + FOR) at comparable doses would be relevant comparators.

7.5 The PBAC noted the data presented from four head-to-head randomised trials comparing BEC/FOR as maintenance treatment to FP/SAL (Papi 2007a, Hsieh 2017), BUD/FOR (Papi 2007b), and BEC + FOR administered via separate inhalers (Huchon 2009). The PBAC considered that the data presented adequately supported the claim of non-inferior comparative effectiveness and safety for the maintenance treatment of asthma in adults.

7.6 The PBAC noted that the submission presented a cost-minimisation analysis between medium dose BEC/FOR and the nominated comparators and that subsequently the pre-PBAC response proposed that BEC/FOR be priced against BUD/FOR 200/6 dry powder inhaler (DPI). The PBAC considered that the cost-minimisation analysis for BEC/FOR use in the maintenance treatment of asthma in adults should be against the least costly ICS/LABA FDC or combination of the individual components (BEC + FOR) that provided a treatment duration of 30 days at the equi-effective doses outlined in paragraph 6.25.

7.7 The PBAC noted the concerns with the financial estimates raised regarding substitution with ICS/LABA FDCs and the potential for use in mild asthma outside of the requested PBS restriction (see paragraphs 6.38 and 6.40). The PBAC considered these were addressed by the Committee's recommendations that listing for the maintenance treatment of asthma should be on a cost-minimisation basis against the least costly ICS/LABA combination as outlined in the paragraph 7.6 and the amendments to the proposed PBS restriction outlined in paragraph 7.11.

[redacted]

7.9 The PBAC noted that the July 2020 update of the Australian Asthma Handbook will include BUD/FOR use as anti-inflammatory reliever therapy in patients with mild asthma. 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.

7.10 The PBAC noted the data presented from the randomised trial comparing BEC/FOR as MART to BEC/FOR plus as needed salbutamol (Papi 2013). The PBAC considered the data presented showed that patients receiving BEC/FOR as MART significantly reduced the time to first severe exacerbation compared to BEC/FOR maintenance plus as-needed salbutamol, but also resulted in more treatment-related AEs (4.4% vs. 2.2%). 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. The PBAC noted the submission did not make a clinical claim for use in MART and considered that the data presented were not adequate to support a listing for this indication.

7.11 The PBAC considered the addition of the administrative note 'This product is not PBS-subsidised for use as "maintenance and reliever" therapy' to the restriction appropriate to highlight the Committee's recommendation regarding MART. The PBAC also suggested the addition of the administrative note 'This product is not PBS-subsidised for use as "anti-inflammatory reliever therapy" for mild asthma' to reduce the risk of inappropriate BEC/FOR use in mild asthma.

7.12 The PBAC recommended that under Section 101(3BA) of the *National Health Act, 1953* BEC/FOR use for maintenance treatment of asthma should be treated as interchangeable on an individual patient basis with other appropriate ICS/LABA FDC products on the PBS.

7.13 The PBAC advised that BEC/FOR is suitable for prescribing by nurse practitioners.

7.14 The PBAC recommended that the Early Supply Rule should not apply.

7.15 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 FP/SAL, 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.

7.16 The PBAC noted that this submission is not eligible for an Independent Review, as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

Add new medicinal product as follows:

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
BECLOMETASONE + FORMOTEROL (EFORMOTEROL) beclometasone dipropionate 100 microgram/actuation + formoterol (eformoterol) fumarate dihydrate 6 microgram/actuation inhalation, 120 actuations	NEW	1	1	5	Fostair

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

Concept ID	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners ☒Nurse practitioners
	Restriction Type / Method: ☒ Authority Required – Streamlined (new code)
9277	**Indication:** Asthma
	Treatment Phase:[blank]
9917	**Clinical criteria:**
9538	Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids
	AND
8384	**Population criteria:**
8383	Patient must be aged 18 years or older.
22301	**Administrative Advice:** This product is not indicated for the initiation of treatment in asthma.
10615	**Administrative Advice:** This drug is not PBS-subsidised for the treatment of chronic obstructive pulmonary disease (COPD)
22302	**Administrative Advice:** Patient must not be on a concomitant single agent long-acting-beta-2-agonist (LABA)
21822	**Administrative Advice:** A LABA includes olodaterol, indacaterol, salmeterol, formoterol or vilanterol.
21825	**Administrative Advice:** Adherence to current treatment and device (inhaler) technique should be reviewed at each clinical visit and before "stepping up" a patient's medication regimen.
new	**Administrative Note:** This product is not PBS-subsidised for use as 'maintenance and reliever' therapy.
new	**Administrative Note:** 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

Chiesi Australia thanks the PBAC for the recommendation and look forward to working on future listings for Fostair.

In relation to paragraphs 7.2 and 7.9, Chiesi Australia notes that FOSTAIR has been available in the EU for more than 7 years (in MART) where SYMICORT and other reliever medications already exist. Also, the TGA have approved use of FOSTAIR as MART.

The National Asthma Council has recently recommended Fostair as MART in the Australian Asthma Handbook. The NAC has since included Fostair as MART in the updated Asthma Handbook (1st September 2020).