

**5.04 BECLOMETASONE WITH FORMOTEROL,
Pressurised inhalation containing beclometasone
dipropionate 200 micrograms and formoterol
fumarate dihydrate 6 micrograms per dose, 120
doses,
Fostair® 200/6,
Chiesi Australia Pty Ltd.**

1 Purpose of submission

- 1.1 The Category 2 submission requested an Authority Required (STREAMLINED) listing for Fostair® metered dose inhaler (MDI), a fixed dose combination (FDC) of beclometasone (BEC), an inhaled corticosteroid (ICS) with formoterol (FOR), a long-acting beta agonist (LABA) as maintenance treatment of asthma.
- 1.2 The proposed listing was for one strength: high dose BEC/FOR (200/6 µg). Low dose BEC/FOR (100/6 µg) is currently listed on the PBS for asthma.
- 1.3 If listed, BEC/FOR (200/6 µg) will be one of six high dose ICS/LABA FDCs available on the PBS for asthma. All ICS/LABA FDCs available on the PBS for asthma are delivered via MDI and/or dry powder inhaler (DPI).
- 1.4 Listing was requested on the basis of a cost-minimisation analysis versus high dose fluticasone propionate (FP) with salmeterol (SAL) FDC. The submission also presented a cost-minimisation analysis versus the individual components of BEC and FOR administered concomitantly via separate inhalers and four other PBS listed high dose ICS/LABA FDCs.

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 beta2 agonist, or patients already adequately controlled on both ICS and LABAs.
Intervention	BEC/FOR 200/6 µg per actuation. For maintenance therapy, two inhalations twice daily (maximum daily dose of 4 inhalations).
Comparator	<p>Main comparator: FP/SAL</p> <ul style="list-style-type: none"> FP/SAL 500/50 µg, 2 inhalations per day (Seretide® Accuhaler®; Pavtide® Accuhaler®) FP/SAL 250/25 µg, 4 actuations per day (Seretide® MDI, Evocair® MDI; Fluticasone + Salmeterol Cipla; Pavtide®; SalplusF® Inhaler; Seroflo®) <p>Secondary comparator: BEC monotherapy</p> <ul style="list-style-type: none"> BEC 100 µg, 8 actuations per day <p>Alternative therapies:</p> <ul style="list-style-type: none"> BEC 100 µg, 8 actuations per day and FOR 6 µg, 4 actuations per day administered concomitantly via separate inhalers ^a MF/IND 260/125 µg, 1 capsule/day FP/FOR, 250/10 µg, 4 actuations per day BUD/FOR 400/12 µg, 4 inhalations per day and BUD/FOR 200/6 µg, 8 actuations per day FF/VI 200/25 µg, 1 inhalation/day
Outcomes	<p>Primary outcomes ^b:</p> <ul style="list-style-type: none"> Morning pre-dose PEF Change from baseline in FEV1 at 5 min post-dose <p>Secondary outcomes (patient-relevant):</p> <ul style="list-style-type: none"> Asthma control Day and night clinical symptoms Asthma exacerbations
Clinical claims	<ol style="list-style-type: none"> BEC/FOR 200/6 µg (4 actuations/day) is non-inferior in terms of efficacy and safety compared to FP/SAL 500/50 µg (2 actuations per day) for the treatment of asthma (based on Study CT-01). BEC/FOR 200/6 µg (4 actuations/day) is superior in terms of efficacy and non-inferior in terms of safety compared to BEC monotherapy 100 µg (8 actuations per day) for the treatment of asthma (based on Study CT-02).

Source: Table 1, pp3-4 of the submission.

BEC = beclometasone dipropionate; BUD = budesonide; FEV1 = forced expiratory volume in one second; FOR = formoterol fumarate dihydrate; FF = fluticasone furoate; FP = fluticasone propionate; ICS = inhaled corticosteroid; IND = indacaterol; LABA = long-acting beta2-agonist; MDI = metered dose inhaler; MF = mometasone furoate; PEF = peak expiratory flow; SAL = salmeterol VI = vilanterol.

^a Referred to as a secondary economic comparator in the submission

^b The co-primary outcomes in the CT-01 trial were change in pre-dose morning FEV1 and change in percentage of complete days without asthma symptoms. The primary outcome in the FORCE/CT-02 trial was change in average pre-dose morning PEF.

2 Background

Registration status

- 2.1 TGA status at time of PBAC advice:** The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration, the TGA Delegate's Overview was available. BEC/FOR 200/6 µg was registered in the European Union in July 2015.
- 2.2** The proposed TGA indication for asthma for BEC/FOR 200/6 µg is "adults (18 years and older) in the 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)".

3 Requested listing

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

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
BECLOMETASONE + FORMOTEROL (EFORMOTEROL)					
<i>beclometasone dipropionate 200 microgram/actuation + formoterol (eformoterol) fumarate dihydrate 6 microgram/actuation inhalation, 120 actuations</i>	NEW	1	1	5	<i>Fostair 200/6</i>
Restriction Summary [11014] / Treatment of Concept: [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) /existing code 11057				
9277	Indication: Asthma				
	Treatment Phase: Initial and continuing				
9539	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.				
28690	Administrative Advice: <i>This pharmaceutical benefit is not for the treatment of chronic obstructive pulmonary disease (COPD).</i>				
22302	Administrative Advice: The patient must not be on a concomitant single agent long-acting-beta-2-agonist (LABA).				
21822	Administrative Advice: A LABA includes olodaterol, indacaterol, salmeterol, formoterol or vilanterol.				
21825	Administrative Advice: Adherence to current treatment and device (inhaler) technique should be reviewed at each clinical visit. and before "stepping up" a patient's medication regimen.				
26570	Administrative Advice: <i>This product is not PBS subsidised for use as 'maintenance and reliever' therapy.</i>				
26584	Administrative Advice: <i>This product is not PBS-subsidised for use as 'anti-inflammatory reliever' therapy for mild asthma.</i>				

3.2 The submission requested a General Schedule, Authority Required (STREAMLINED) listing of high dose beclometasone and formoterol (BEC/FOR 200/6 µg) for the maintenance therapy treatment of asthma in patients aged 18 years and older. The PBAC advised an Authority Required (STREAMLINED) listing would be appropriate and

would be consistent with the main comparator, fluticasone propionate 500 microgram/actuation + salmeterol 50 microgram/actuation (FP/SAL 500/50 µg), and the current listing of medium dose beclometasone and formoterol (BEC/FOR 100/6 µg).

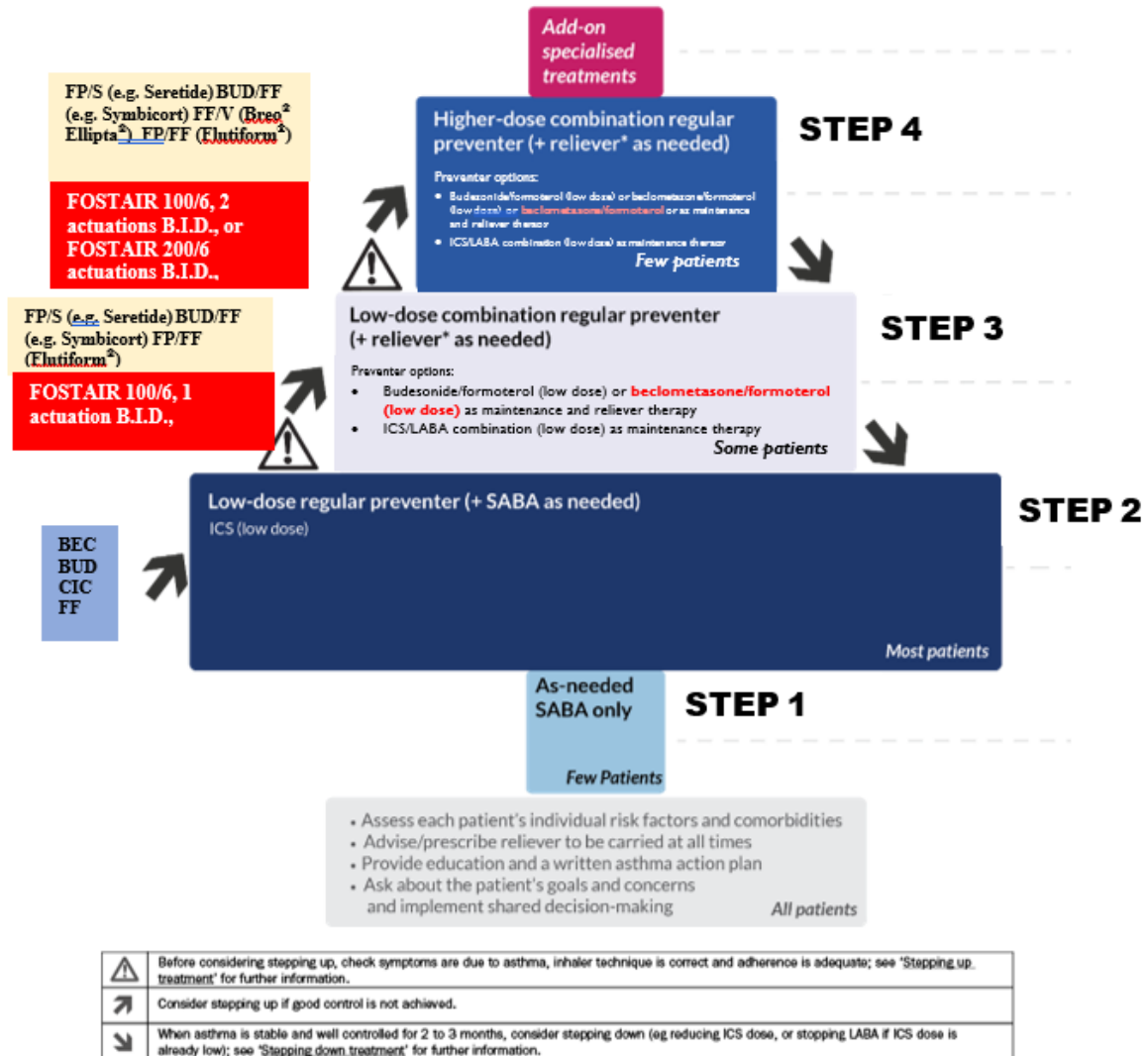
- 3.3 The PBAC advised the following Administrative Advice should be included in the restriction of BEC/FOR 200/6 µg:
- This pharmaceutical benefit is not for the treatment of chronic obstructive pulmonary disease (COPD).
 - This product is not PBS-subsidised for use as 'anti-inflammatory reliever' therapy for mild asthma.
 - This product is not PBS-subsidised for use as 'maintenance and reliever' therapy' (MART). Although BEC/FOR 100/6 µg was TGA approved to be used as a MART, the PBAC advised previously that BEC/FOR 100/6 µg should not be subsidised for MART due to concerns the data presented was not adequate to support a listing for this indication and the potential for quality use of medicine issues (paragraphs 7.09-7.11, beclometasone with formoterol, Public Summary Document (PSD), July 2020 PBAC meeting). The PBAC therefore advised the same Administrative Advice should be included in the restriction for BEC/FOR 200/6 µg, given that the submission for BEC/FOR 200/6 µg is not requesting TGA or PBAC approval to be used as a MART.
- 3.4 Consistent with BEC/FOR 100/6 µg and other high dose asthma drugs, the submission requested to include the following 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'. Unlike the dose instruction for BEC/FOR 100/6 µg, there is no approved dose increase with BEC/FOR 200/6 µg according to the proposed Product Information (the maximum daily dose is 4 inhalations). Note that BEC/FOR 200/6 µg is currently undergoing TGA evaluation, and this may be updated prior to TGA approval. The PBAC advised it was appropriate to include the same Administrative Advice to be consistent with other asthma listings.
- 3.5 The submission did not propose any special pricing arrangements.
- 3.6 The PBAC noted the sponsor will update the trade name of BEC/FOR 100/6 µg 'FOSTAIR' to 'Fostair 100/6' for consistency with the trade name of BEC/FOR 200/6 µg 'Fostair 200/6'.

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, chest tightness) that vary over time. The primary goal of asthma pharmacotherapy is to reduce the underlying inflammation and promote bronchodilation.
- 4.2 Asthma severity is determined by the type and amount of treatment needed to maintain adequate symptom control, with more serious disease requiring a greater intensity of treatment. Pharmacological management involves a stepwise approach for mild to moderate asthma and a targeted approach for severe asthma.
- 4.3 The clinical management algorithm presented in the submission was based on the stepped pharmacological treatment algorithm presented in the Australian Asthma Handbook version 2.0 (2019) (see **Error! Reference source not found.**). The submission proposed that BEC/FOR 200/6 µg would be an alternative high dose ICS/LABA treatment for patients in 'Step 4'.

Figure 1 Clinical management algorithm proposed in the submission



ICS include beclomethasone dipropionate (beclomethasone dipropionate), budesonide (BUD), ciclesonide (CIC), fluticasone fumarate (FF), fluticasone propionate (FP). ICS/LABA combination products include budesonide (BUD)/formoterol fumarate (FF), fluticasone propionate (FP)/salmeterol, fluticasone furoate (FF)/vilanterol (V), and beclomethasone dipropionate (beclomethasone dipropionate)/formoterol fumarate (FF) (FOSTAIR).

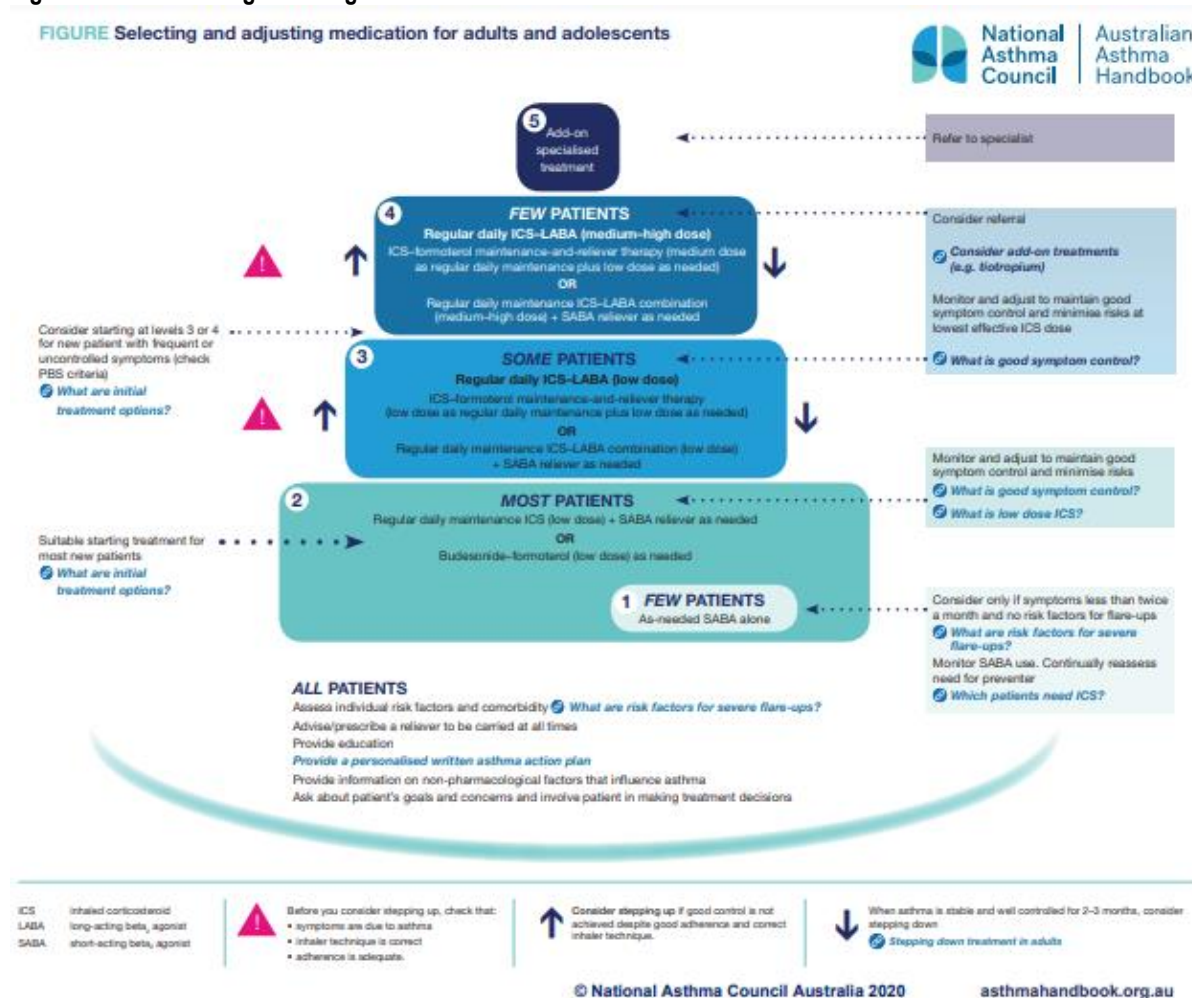
Source: Figure 12, p29 of the submission, based on the Australian Asthma Handbook version 2.0, published March 2019.

4.4 Version 2.1 of the Australian Asthma Handbook (published September 2020) includes an updated treatment algorithm (see **Error! Reference source not found.**). The clinical algorithm and associated discussion presented by the submission does not include the following components of the treatment algorithm presented in the Australian Asthma Handbook (2020):¹

¹ National Asthma Council. Australian Asthma Handbook. Version 2.1. September 2020. https://d30b7srod7pe7m.cloudfront.net/uploads/Figure_Selecting-and-adjusting-medication-for-adults-and-adolescents_web.pdf [accessed 22-Mar-22]

- the role of budesonide + formoterol (low dose) in Step 2,
- the role of add-on treatments (e.g., tiotropium) in Step 4, and
- subsequent treatments (e.g., antibody therapy) in Step 5.

Figure 2 Clinical management algorithm in current Australian Asthma Handbook



Source: Australian Asthma Handbook version 2.1, published September 2020.

4.5 The treatment algorithm presented in the submission was not current. The omission of budesonide + formoterol (low dose) in Step 2 and subsequent treatments in Step 5 are unlikely to be important for this submission. However, the role of add-on treatments (tiotropium, a long-acting muscarinic antagonist (LAMA)) and, by extension, FDC triple therapies (e.g., mometasone + indacaterol + glycopyrronium and beclometasone + formoterol + glycopyrronium) is relevant. In clinical practice, patients may transition from medium dose ICS/LABA to medium dose ICS/LABA/LAMA rather than high dose ICS/LABA to maintain symptom control and minimise adverse events by using the lowest effective ICS dose.¹ Transitioning from medium dose ICS/LABA to medium dose ICS/LABA/LAMA (not high dose ICS/LABA) is consistent with

Track 1 of the Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention.

- 4.6 The Australian Asthma Handbook also recommended that “if high doses of inhaled corticosteroids are needed, they should be used for short periods only for most patients”.² Furthermore, it listed a range of adverse events that are associated with ICS, such as dysphonia and candidiasis, and noted that long-term use of higher doses of ICS increases the risk of lower bone mineral density, cataracts, and diabetes. These adverse events are also noted in the draft TGA Production Information for BEC/FOR 200/6 µg. Finally, the Australian Asthma Handbook noted that patient concerns regarding ICS are a major reason for poor adherence to asthma medications.

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

5 Comparator

- 5.1 The submission nominated FP/SAL (500/50 µg, two inhalations daily and 250/25 µg, four actuations daily) as the main comparator. The main arguments provided in support of this nomination were:

- The CT-01 head-to-head trial demonstrated that BEC/FOR 200/6 µg was non-inferior to FP/SAL 500/50 µg in terms of both efficacy and safety.
- FP/SAL (500/50 µg, two inhalations daily and 250/25 µg, four actuations daily) has the highest PBS utilisation market share for high dose ICS/LABA products for the asthma indication.
- The submission expected FP/SAL (500/50 µg, two inhalations daily and 250/25 µg, four actuations daily) to be the lowest cost alternative therapy by the time of the July 2022 PBAC meeting due to the FP/SAL (500/50 µg, two inhalations daily and 250/25 µg, four actuations daily) prices being reduced from \$46.78 (DPMQ \$62.38) to \$40.86 (DPMQ \$56.01) in the April 2022 price disclosure cycle. The prices of FP/SAL (500/50 µg and 250/25 µg) were not reduced on 1st April 2022 following confirmation of the April 2022 price disclosure outcomes. Consequently, FP/SAL is not the lowest cost alternative therapy.
- Two other dual ICS/LABA FDCs, fluticasone propionate + formoterol (FP/FOR 250/10 µg, four inhalations daily) and fluticasone furoate + vilanterol (FF/VI 200/25 µg, one inhalation daily) were previously recommended by the PBAC with FP/SAL (500/50 µg, two inhalations daily and 250/25 µg, four actuations daily) as the main comparator.

² National Asthma Council. Australian Asthma Handbook. Version 2.1. September 2020. <https://www.asthmahandbook.org.au/management/adults/stepped-adjustment/stepping-up> [accessed 1-Apr-22]

- 5.2 The main comparator is appropriate on the basis of it having the highest market share. The additional arguments are not directly relevant to the selection of the comparator based on the PBAC guidelines. However, the additional arguments are relevant for identifying relevant alternative therapies as per Section 101(3B) of the *National Health Act 1953*.
- 5.3 The submission also nominated BEC monotherapy (100 µg, eight actuations daily) as a secondary clinical comparator as the basis for establishing at least an additive beneficial effectiveness. The main argument provided in support of this nomination was that the CT-02 trial demonstrated the superiority of BEC/FOR (200/6 µg, four actuations daily) versus BEC monotherapy. The secondary clinical comparator is reasonable.
- 5.4 Medium dose ICS/LABA/LAMA treatment may be an informative comparator to high dose ICS/LABA – to assess the relative benefit of adding LAMA therapy versus increasing the ICS dose (see paragraph 4.5 for discussion). Mometasone with indacaterol and glycopyrronium (MF/IND/GLY) is the only medium dose ICS/LABA/LAMA therapy currently listed on the PBS for asthma.
- 5.5 For the requested population, the following PBS-listed medicines may be considered alternative therapies because they could be replaced in practice: FP/SAL, MF/IND, FP/FOR, BUD/FOR and FF/VI.
- 5.6 The table below presents the main comparator and alternative therapies identified in the submission.

Table 2: PBS-listed medicines that may be considered alternatives to the intervention (BEC/FOR 200/6 µg)

PBS Items	Brand(s)	Medicine Strength and Form	Days per inhaler	Included in clinical comparison	Included in economics section	Included in financial estimates
High dose ICS/LABA dual therapy						
8432T	Seretide® Accuhaler®, Pavtide® Accuhaler®	Fluticasone 500 µg /actuation + salmeterol 50 µg /actuation powder for inhalation, 60 actuations • FP/SAL (500/50 µg)	30	Yes	Yes	Yes
8519J	Seretide® MDI, Seroflo®, SalpusF® inhaler, Pavtide®, Fluticasone + Salmeterol Cipla, Evocair® MDI	Fluticasone 250 µg /actuation + salmeterol 25 µg /actuation inhalation, 120 actuations • FP/SAL (250/25 µg)	30	Yes	Yes	Yes
8750M, 11301T	Symbicort® Turbuhaler®, BiResp Spiromax®, DuoResp Spiromax®	Budesonide 400 µg /actuation + formoterol fumarate dihydrate 12 µg /actuation powder for inhalation, 2 x 60 actuations • BUD/FOR (400/12 µg)	30	No	Yes	Yes
10018G, 12082X ^a	Symbicort® Rapihaler®,	Budesonide 200 µg /actuation + formoterol fumarate dihydrate 6 µg /actuation inhalation, 120 actuations • BUD/FOR (200/6 µg)	15	No	Yes	Yes
10008R	Flutiform®	fluticasone propionate 250 µg /actuation + formoterol fumarate dihydrate 10 µg /actuation inhalation, 120 actuations • FP/FOR (250/10 µg)	30	No	Yes	Yes
11129R	Breo Ellipta®	fluticasone furoate 200 µg /actuation + vilanterol 25 µg /actuation powder for inhalation, 30 actuations • FF/VI (200/25 µg)	30	No	Yes	Yes
12279G	Atectura® Breezhaler®	indacaterol 125 µg + mometasone furoate 260 µg powder for inhalation, 30 capsules • MF/IND (260/125 µg)	30	No	Yes	Yes

Source: Tables 4, 67 & 70, pp20-21, 112-113, & 117 of the submission; PBS website (accessed 22-Mar-22); Symbicort Rapihaler PI; Symbicort Turbuhaler PI; BiResp Spiromax PI

BEC = beclometasone dipropionate; FOR = formoterol fumarate dihydrate; ICS = inhaled corticosteroid; LABA = long-acting beta agonist; MDI = metered dose inhaler; PBS = Pharmaceutical Benefits Scheme.

^a There are five additional PBS items for BUD/FOR 200/6 µg, none of which are relevant to this application: 12029D & 12041R are for patients with mild asthma who require an anti-inflammatory reliever therapy, 12093L is for patients who have failed FP/SAL, 8625Y & 11273H are not indicated for 8 inhalations daily.

^b The submission noted that beclometasone has two 100 µg presentations on the PBS, (Item 8407L AEMP \$17.77 and 16,713 services in 2020/21 and Item 8409N AEMP \$21.49 and 6,466 services in 2020/21) (p112 of the submission). The cheaper and more prescribed PBS Item 8407L was used in the cost-minimisation analysis.

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 a consumer group/organisation (1) via the Consumer Comments facility on the PBS website. Asthma Australia supported the listing of BEC/FOR 200/6 µg for asthma, highlighting it would be recommended mostly for patients uncontrolled on low or medium-dose ICS-LABA; or considered where a patient has been using medium or high dose ICS monotherapy and continues to experience poor symptom control. Asthma Australia noted it would be an appropriate and recommended option for patients uncontrolled on BEC/FOR 100/6 µg that are already familiar with the device and treatment regimen.

Clinical trials

6.3 The submission was based on the following trials involving BEC/FOR 200/6 µg:

- One randomised trial comparing BEC/FOR (200/6 µg, four actuations daily), non-extrafine BEC monotherapy (250 µg, eight actuations daily) and FP/SAL (500/50 µg, two inhalations daily) in severe persistent asthma patients: CT-01 (N=721).
- One randomised trial comparing BEC/FOR (200/6 µg, four actuations daily) and extrafine BEC monotherapy (100 µg, eight actuations daily) in moderate to severe asthma: FORCE/CT-02 (N=376).

6.4 Details of the trials presented in the submission are provided in the table below.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
CT-01 EUCTR2007-002587-99	A 24-week, multicenter, multinational, randomised, double-blind, triple-dummy, 3-arm parallel group study comparing the efficacy and safety of CHF 1535 200/6 (beclomethasone dipropionate 200 µg plus formoterol 6 µg/actuation), 2 puffs b.i.d., versus beclomethasone dipropionate HFA (250 µg/actuation), 4 puffs b.i.d., versus Seretide® 500/50 (fluticasone 500 µg plus salmeterol 50 µg/actuation), 1 inhalation b.i.d., in patients with severe asthma.	03 November 2010
FORCE/CT-02 NCT01577082 EUCTR2010-020602-14	A 12-week, multinational, multicentre, randomised, double-blind, double-dummy, 2-arm parallel group study comparing the efficacy and safety of CHF 1535 200/6 µg (fixed combination beclomethasone dipropionate / formoterol) versus beclomethasone dipropionate in adult asthmatic patients not adequately controlled on high doses of inhaled corticosteroids or on medium dose of inhaled corticosteroids plus long-acting β2-agonists. Paggiaro P, Corradi M, Latorre M, Raptis H, Muraro A, Gessner C, Siergiejko Z, Scuri M, Petruzzelli S. High strength extrafine pMDI beclomethasone/formoterol (200/6 µg) is effective in asthma patients not adequately controlled on medium-high dose of inhaled corticosteroids. Paggiaro P, Corradi M, Raptis H, Baronio R, Gessner C, Siergiejko Z, Scuri M, Petruzzelli S. High dose extrafine beclomethasone/formoterol via metered dose inhaler is effective and safe in asthmatics not controlled on medium-high dose of inhaled corticosteroids.	09 April 2014 <i>BMC Pulmonary Medicine</i> 2016; 16(1): 1-9. <i>European Respiratory Journal</i> 2014; 44(Suppl 58).

Source: Table 16, p43 of the submission.

6.5 The key features of the direct randomised trials are summarised in the table below.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Key efficacy outcomes
BEC/FOR (200/6 µg) vs. FP/SAL (500/50 µg) and BEC (250 µg non-extrafine)					
CT-01	721	MC, R, DB 2w run-in + 24w tx	Low	Aged ≥12 and ≤70 years, severe persistent asthma, FEV1 ≥40% and <80%	Co-1°: Change in pre-dose morning FEV1 (24w); percentage of complete days without asthma symptoms (24w). 2°: Change in pre-dose morning PEF; evening PEF; PEF variability; pulmonary function tests; asthma control measures; moderate/severe asthma exacerbations.
BEC/FOR (200/6 µg) vs. BEC (100 µg extrafine)					
FORCE/CT-02	376	MC, R, DB 2w run-in + 12w tx	Low	Aged ≥18 years, asthma not optimally controlled on high dose ICS or medium dose ICS/LABA, FEV1 ≥40% and <80%	1°: Change in pre-dose morning PEF (12w) 2°: Evening PEF: PEF variability; pulmonary function tests (including change in pre-dose morning FEV1); asthma control measures (including percentage of complete days without asthma symptoms); ACQ scores; moderate/severe asthma exacerbations.

Source: Table 17, 20, 27 & 28, pp48-51, 52-53, 67-68 & 70-72 of the submission; pp44-45 of the submission. Italicised text added during the evaluation.

1° = primary; 2° = secondary; Co-1° = co-primary; ACQ = asthma control questionnaire; BEC = beclomethasone dipropionate; DB = double blind; FEV1 = forced expiratory volume in one second; FOR = formoterol fumarate dihydrate; FP = fluticasone propionate; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist; MC = multi-centre; OL = open label; OS = overall survival; PEF = peak expiratory flow; PFS = progression-free survival; R = randomised; SAL = salmeterol; tx = treatment; w = weeks.

- 6.6 The CT-01 and FORCE/CT-02 trials were double blinded, randomised, controlled trials with a parallel-group design. Clinical assessments were made without breaking the blind and all key outcomes were reported. Technically the definition of intent-to-treat (ITT) in the CT-01 and FORCE/CT-02 trials did not match the standard definition of ITT.³ However, since the ITT populations contained 99.3% and 95.9% of participants randomised, respectively, these differences are unlikely to affect the results.⁴
- 6.7 The duration of the trials was short (12 to 24 weeks) compared to the chronic nature of asthma. However, the Australian Asthma Handbook recommended that high dose ICS should be used for short periods of time.⁵ This was due to the increased risk of adverse events with long-term use of higher doses.
- 6.8 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). These outcomes were measured across the trials.
- 6.9 The submission proposed a non-inferiority margin for adjusted mean change in pre-dose morning FEV1 from baseline to visit 7 (week 24) of -0.20 L, based on the CT-01 trial. The PBAC has previously accepted a non-inferiority margin of -0.20 L for this outcome (paragraph 8, fluticasone propionate with eformoterol fumarate, PSD, July 2013 PBAC meeting; paragraphs 6.9 and 7.5, beclometasone dipropionate with formoterol fumarate dihydrate, PSD, July 2020 PBAC meeting).
- 6.10 The submission did not propose a non-inferiority margin for the other co-primary outcome in the CT-01 trial (percentage of complete days without asthma symptoms). A minimum clinically important difference (MCID) of $\geq 20\%$ reduction in annual rates of severe asthma exacerbation has previously been proposed for ICS/LABA therapies, however the ESC considered that in terms of clinical relevance, smaller than a 20% reduction in severe exacerbation rates may represent a clinically meaningful difference, given the seriousness of the exacerbations (paragraph 6.14, budesonide with formoterol, PSD, July 2019 PBAC meeting).
- 6.11 The ESC has previously considered differences in morning PEF up to 16 L/min unlikely to be clinically relevant (paragraphs 6.16, 6.18 & 6.19, mometasone furoate with

³ Hollis, Sally; Campbell, Fiona (September 1999). "What is meant by intention to treat analysis? Survey of published randomised controlled trials". *BMJ*. 319 (7211): 670–674

⁴ The RoB 2 guidance document recommends that "For continuous outcomes, availability of data from 95% of the participants will often be sufficient." Revised Cochrane risk-of-bias tool for randomised trials (RoB 2). 22 August 2019. <https://www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2> [accessed 8-Apr-22]

⁵ National Asthma Council. Australian Asthma Handbook. Version 2.1. September 2020. <https://www.asthmahandbook.org.au/management/adults/stepped-adjustment/stepping-up> [accessed 1-Apr-22]

indacaterol, PSD, July 2020 PBAC meeting). Further, a non-inferiority margin for the difference in morning pre-dose PEF of -20 L/min was considered to be reasonable in the evaluation of BEC/FOR 100/6 µg (paragraph 6.8, beclometasone dipropionate with formoterol fumarate dihydrate, PSD, July 2020 PBAC meeting).

Comparative effectiveness

6.12 The key results for the CT-01 trial at 24 weeks are summarised in the table below. The results of the comparison between BEC/FOR 200/6 µg and BEC 250 µg non-extrafine are not presented for brevity.

Table 5: Key efficacy outcomes reported in the CT-01 Trial (ITT population)

Outcome	BEC/FOR (200/6 µg)	FP/SAL (500/50 µg)	Treatment difference (Mean, 95% CI)	p-value	Direction of difference
Primary outcomes					
Change in pre-dose morning FEV1 (L) (Adjusted mean change, 95% CI) ^a	0.20 (0.14, 0.25)	0.22 (0.17, 0.28)	-0.03 (-0.10, 0.05)	0.489	<i>Favours comparator</i>
Change in % days without asthma symptoms (Adjusted mean change, 95% CI) ^a	24.64% (19.05, 30.24)	26.57% (21.13, 32.01)	-1.93% (-9.74, 5.89)	0.628	<i>Favours comparator</i>
Secondary outcomes					
Change in pre-dose morning PEF (L/min) (Adjusted mean change, 95% CI) ^a	15.99 (9.06, 22.92)	16.14 (9.79, 22.49)	-0.15 (-9.59, 9.30)	0.975	<i>Favours comparator</i>
Moderate/severe asthma exacerbations n/N, % (95% CI)	16/234, 6.8% (4.3, 10.8)	19/241, 7.9% (5.1, 12.0)	-1.1%	NR	<i>Favours BEC/FOR</i>

Source: Tables 36, 40 & 46, pp76, 79 & 85 of the submission; Tables 4.2.1 & 4.3.1, pp1234 & 1274-1275 of the CT-01 CSR. Italicised text added during the evaluation.

BEC = beclometasone dipropionate; CI = confidence interval; FEV1 = forced expiratory volume in one second; FOR = formoterol fumarate dihydrate; FP = fluticasone propionate; ITT = intention to treat; L = litres; min = minute; n = number of participants reporting data; N = total participants in group; NR = not reported; PEF = peak expiratory flow; SAL = salmeterol.

^a Adjustments made using an ANCOVA model including baseline as covariate and terms for treatment group and country.

6.13 In the CT-01 trial, the estimated treatment difference between BEC/FOR 200/6 µg and FP/SAL 500/50 µg was -0.03 L (95% confidence interval, CI: -0.10, 0.05). The submission stated that non-inferiority of BEC/FOR 200/6 µg was proven since the lower 95% CI for treatment difference was above the pre-specified non-inferiority margin of -0.20 L.

6.14 In the CT-01 trial, the estimated treatment difference between BEC/FOR 200/6 µg and FP/SAL 500/50 µg for change in percentage of days without asthma symptoms was -1.93% (95% CI: -9.74, 5.89). Change in percentage days without asthma symptoms from baseline to end of treatment was a co-primary outcome of the CT-01 trial. However, since superiority to BEC 250 µg non-extrafine could not be proven, the comparison of change in percentage days without asthma symptoms from baseline to end of treatment (week 24) for BEC/FOR 200/6 µg and FP/SAL 500/50 µg was considered exploratory as per the statistical analysis plan.

6.15 No statistically significant differences between treatment arms were identified between BEC/FOR 200/6 µg and FP/SAL 500/50 µg in the key secondary outcomes presented in Table 5. Asthma Control Questionnaire (ACQ) scores were not measured in the CT-01 trial.

6.16 The key results for the FORCE/CT-02 trial at 12 weeks is summarised below

Table 6: Key efficacy outcomes reported in the FORCE/CT-02 trial (ITT population)

Outcome	BEC/FOR (200/6 µg)	BEC (100 µg extrafine)	Treatment difference (Mean, 95% CI)	p-value	Direction of difference
Primary outcome					
Change in pre-dose morning PEF (L/min) (Adjusted mean change, 95% CI) ^a	17.63 (11.58, 23.68)	-0.90 (-7.26, 5.46)	18.53 (10.33, 26.73)	<0.001	<i>Favours BEC/FOR</i>
Secondary outcomes					
Change in pre-dose morning FEV1 (L) (Adjusted mean change, 95% CI) ^b	0.28 (0.23, 0.34)	0.21 (0.16, 0.27)	0.07 (-0.002, 0.145)	0.058	<i>Favours BEC/FOR</i>
Change in % days without asthma symptoms ^a (Adjusted mean change, 95% CI)	10.32% (6.95, 13.69)	11.74% (8.23, 15.24)	-1.42% (-5.97, 3.13)	0.540	<i>Favours comparator</i>
Change in ACQ scores (adjusted mean change, 95% CI) ^{a, c}	-0.69 (-0.78, -0.60)	-0.69 (-0.79, -0.59)	-0.00 (-0.13, 0.12)	0.961	<i>Favours comparator</i>
Moderate/severe asthma exacerbations n/N, %	4/184 2.2%	6/175 3.4%	-1.2%	NR	<i>Favours BEC/FOR</i>

Source: Tables 47, 48, 54, 56 & 57, pp86, 87, 93-95 of the submission. **Bold indicates statistically significant result.** Italicised text added during the evaluation.

ACQ = asthma control questionnaire; BEC = beclometasone dipropionate; CI = confidence interval; FEV1 = forced expiratory volume in one second; FOR = formoterol fumarate dihydrate; ITT = intention to treat; L = litres; min = minute; n = number of participants reporting data; N = total participants in group; NR = not reported; PEF = peak expiratory flow.

^a Adjustments made using an ANCOVA model with change from baseline to the entire treatment period in average pre-dose morning PEF as dependent variable and treatment, country, and sex as factors and baseline as a covariate.

^b Performed using a linear MMRM with treatment, visit, treatment x visit interaction, country and sex as fixed effects, and baseline and baseline x visit interaction as covariates.

^c The ACQ version (5 item or 7 item) is not specified in the submission or CSR, although the CSR reference (Juniper 1999) relates to the ACQ-7.

Comparative harms

6.17 The results of treatment exposure and safety outcomes in the CT-01 trial are summarised in the table below. The results of the comparison between BEC/FOR 200/6 µg and BEC 250 µg non-extrafine are not presented for brevity.

Table 7: Summary of key adverse events in the CT-01 trial (Safety population)

Trial ID	CT-01		
	BEC/FOR 200/6 µg	FP/SAL 500/50 µg	p-value for comparison
N	239	242	
Treatment exposure, days			
Mean	151.50 ± 42.60	150.70 ± 45.40	-
Range	9-177	2-177	-
Summary safety outcomes, n (%)			
Number of patients with ≥1 TEAEs	89 (37.20)	90 (37.20)	0.991
Severe TEAEs	5 (2.10)	5 (2.10)	1.000
Number of patients with ≥1 serious TEAEs	5 (2.10)	4 (1.70)	0.750
Discontinuations due to TEAEs	3 (1.30)	2 (0.80)	0.684
Deaths due to TEAEs	0 (0)	0 (0)	1.000
Number of patients with ≥1 ADR	21 (8.80)	20 (8.30)	0.838
Severe ADRs	0 (0)	0 (0)	1.000
TEAEs occurring in ≥3% patients, n (%)			
Asthma	21 (8.80)	21 (8.70)	0.966
Nasopharyngitis	9 (3.80)	16 (6.60)	0.160
Headache	9 (3.80)	6 (2.50)	0.417
Cough	6 (2.50)	8 (3.30)	0.614
TEAEs of special interest, n (%)^a			
Dysphonia	4 (1.70)	7 (2.90)	0.371
Candidiasis	1 (0.40)	7 (1.00)	1.000

Source: Tables 23, 26 & 58-61, pp56 & 96-97 of the submission; pp1503, 1525, 1527 & 1528 of the CT-01 CSR. Italicised text added during the evaluation using data from the CT-01 CSR.

ADR = adverse drug reaction; BEC = beclometasone dipropionate; CI = confidence interval; FOR = formoterol fumarate dihydrate; FP = fluticasone propionate; n = number of participants reporting data; N = total participants in group; NR = not reported; SAL = salmeterol; TEAE = treatment-emergent adverse event.

^a Hoarseness (dysphonia) and candidiasis are the most common local adverse effects of inhaled corticosteroids.⁶

6.18 The results of treatment exposure and safety outcomes in the FORCE/CT-02 trial are summarised in the table below.

⁶ National Asthma Council. Australian Asthma Handbook. Version 2.1. September 2020. <https://www.astmahandbook.org.au/management/adults/stepped-adjustment/stepping-up> [accessed 5-Apr-22]

Table 8: Summary of key adverse events in the FORCE/CT-02 trial (Safety population)

Trial ID	FORCE/CT-02	
	BEC/FOR 200/6 µg	BEC 100 µg extrafine
Medicine		
N	189	180
Treatment exposure, days		
Mean	81.0 ± 16.8	79.7 ± 19.3
Range	1-92	1-95
Summary safety outcomes, n (%)		
Number of patients with ≥1 TEAEs	29 (15.30)	30 (16.70)
Severe TEAEs	0 (0)	0 (0)
Number of patients with ≥1 serious TEAEs	0 (0)	0 (0)
Discontinuations due to TEAEs	0 (0)	1 (0.60)
Deaths due to TEAEs	0 (0)	0 (0)
Number of patients with ≥1 ADR	2 (1.1)	5 (2.8)
Severe ADRs	0 (0)	0 (0)
TEAEs occurring in ≥3% patients, n (%)		
Asthma	5 (2.60)	7 (3.90)
Nasopharyngitis	7 (3.70)	5 (2.80)
Headache	2 (1.10)	3 (1.70)
Cough	1 (0.50)	0 (0)
TEAEs of special interest, n (%)^a		
Dysphonia	0 (0)	1 (0.60)
Candidiasis	1 (0.50)	0 (0)

Source: Tables 23, 26 & 58-61, pp 59 & 98-99 of the submission; p84 of the CT-02 CSR. Italicised text added during the evaluation using data from the CT-02 CSR.

ADR = adverse drug reaction; BEC = beclometasone dipropionate; CI = confidence interval; FOR = formoterol fumarate dihydrate; n = number of participants reporting data; N = total participants in group; TEAE = treatment-emergent adverse event.

^a Hoarseness (dysphonia) and candidiasis are the most common local adverse effects of inhaled corticosteroids.⁷

6.19 The submission also provided details on electrocardiogram (ECG) and serum cortisol measurements in the CT-01 trial (pp97-98 of the submission) and ECG, haematology, and blood chemistry measurements (including serum cortisol) in the FORCE/CT-02 trial (pp98 & 100 of the submission).

6.20 Overall, the adverse event profile of BEC/FOR 200/6 µg was similar to BEC 250 µg non-extrafine and FP/SAL 500/50 µg in the CT-01 trial. The adverse event profile of BEC/FOR 200/6 µg was also similar to BEC 100 µg extrafine in the FORCE/CT-02 trial.

Benefits/harms

6.21 There were no clinically meaningful differences between BEC/FOR 200/6 µg and the main comparator FP/SAL 500/50 µg in efficacy and safety when used for the treatment of asthma.

Clinical claim

6.22 The submission described BEC/FOR (200/6 µg/actuation, two actuations b.i.d.) as:

⁷ National Asthma Council. Australian Asthma Handbook. Version 2.1. September 2020. <https://www.asthmahandbook.org.au/management/adults/stepped-adjustment/stepping-up> [accessed 5-Apr-22]

- Non-inferior in terms of efficacy and safety compared to FP/SAL (500/50 µg/actuation, one inhalation b.i.d.) for the treatment of asthma, based on the results of CT-01 trial.
 - Superior in terms of efficacy and comparable in terms of safety compared to BEC (100 µg extrafine, four actuations b.i.d.) for the treatment of asthma, based on the results of FORCE/CT-02 trial.
- 6.23 The therapeutic conclusion presented in the submission for BEC/FOR compared to FP/SAL was adequately supported by the clinical evidence presented in the submission because:
- BEC/FOR 200/6 µg was shown to be non-inferior to FP/SAL 500/50 µg for the primary outcome of change from baseline to the end of the treatment in pre-dose morning FEV1 at 24 weeks, based on a pre-specified non-inferiority margin of -0.2L in the CT-01 trial.
 - There were no statistically significant differences between BEC/FOR 200/6 µg and FP/SAL 500/50 µg in any of the secondary outcomes reported in the CT-01 trial, and the differences between the treatments appeared small.
 - The number and proportion of patients experiencing adverse events were similar between the BEC/FOR 200/6 µg and FP/SAL 500/50 µg treatment arms, and the treatments were generally well-tolerated. Although the duration of the trial was short, and the Australian Asthma Handbook recommended that high dose ICS should be used for short periods of time.⁸ This was due to the increased risk of adverse events with long-term use of higher doses.
- 6.24 The therapeutic conclusion presented in the submission for BEC/FOR compared to BEC 100 µg extrafine based on the clinical evidence presented is reasonable because:
- BEC/FOR 200/6 µg was shown to be superior to BEC 100 µg for the primary outcome of change from baseline to the end of the treatment in pre-dose morning PEF at 12 weeks in the FORCE/CT-02 trial.
 - While BEC/FOR 200/6 µg was shown to be numerically worse than BEC 100 µg in some secondary outcomes, the differences were not statistically significant (e.g., change in percentage of asthma symptom free days: treatment difference = -1.42 [95%CI: -5.97, 3.13, p = 0.54]).
 - The number and proportion of patients experiencing adverse events were similar between the BEC/FOR 200/6 µg and BEC 100 µg treatment arms, and the treatments were generally well-tolerated. Although the duration of the trial was short, and the Australian Asthma Handbook recommended that high dose ICS

⁸ National Asthma Council. Australian Asthma Handbook. Version 2.1. September 2020. <https://www.asthmahandbook.org.au/management/adults/stepped-adjustment/stepping-up> [accessed 1-Apr-22]

should be used for short periods of time.⁹ This was due to the increased risk of adverse events with long-term use of higher doses.

- 6.25 The submission did not present any evidence to inform the effectiveness and safety of BEC/FOR 200/6 µg against high dose ICS/LABA FDCs other than FP/SAL. Despite this, it may be reasonable to anticipate that high dose BEC/FOR would be similar to other high dose ICS/LABA FDCs based on established equi-potent doses of ICS. This would be similar to a previous decision by the PBAC regarding low dose BEC/FOR (paragraph 6.20, beclometasone dipropionate with formoterol fumarate dihydrate, PSD, July 2020 PBAC meeting).
- 6.26 The submission did not present any evidence to inform the effectiveness and safety of BEC/FOR 200/6 µg against medium dose ICS/LABA/LAMA FDC. The PBAC has not considered any high dose ICS/LABA combinations as treatment for asthma since the consideration of medium dose MF/IND/GLY in July 2020. The March 2022 PSD for BEC/FOR/GLY (100/6/10 µg & 200/6/10 µg) did not make a clinical claim for medium dose ICS/LABA/LAMA versus high dose ICS/LABA. However, that PSD included a systematic review and network meta-analysis comparing medium and high dose ICS/LABA/LAMA to medium and high dose ICS/LAMA (Rogliani 2021)¹⁰. This systematic review found that medium dose ICS/LAMA/LABA was superior to high dose ICS/LABA in terms of change in pre-dose morning FEV1 (relative effect: 58.45, 95% CI: 27.45, 88.78, p<0.05) but not relative risk of moderate/severe asthma exacerbations (relative effect: 1.04, 95% CI: 0.87, 1.26). A randomised Phase IV trial comparing BEC/FOR 200/6 µg against medium dose ICS/LABA/LAMA FDC (BEC/FOR/GLY 100/6/12.5 µg) is currently recruiting and scheduled for completion in July 2023.¹¹
- 6.27 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.
- 6.28 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

- 6.29 The submission presented a cost-minimisation analysis based on the DPMQ between BEC/FOR 200/6 µg and the nominated alternative therapies. The approach taken in

⁹ National Asthma Council. Australian Asthma Handbook. Version 2.1. September 2020. <https://www.asthmahandbook.org.au/management/adults/stepped-adjustment/stepping-up> [accessed 1-Apr-22]

¹⁰ Rogliani P, Ritondo BL, Calzetta L. Triple therapy in uncontrolled asthma: a network meta-analysis of Phase III studies. *Eur Respir J* 2021;58. <https://erj.ersjournals.com/content/early/2021/01/21/13993003.04233-2020> [accessed 8-Apr-22]

¹¹ Step-up to Medium Strength Triple Therapy vs High Strength ICS/LABA in Adult Asthmatics Uncontrolled on Medium Strength ICS/LABA (MiSTIC), <https://clinicaltrials.gov/ct2/show/NCT05018598> [accessed 14-Apr-2022]

the submission was to equalise the cost at DPMQ per 30 days. The analysis assumed no additional costs or cost-offsets.

- 6.30 The cost-minimisation analysis was based on the claim of non-inferior effectiveness and safety for BEC/FOR (200/6 µg/actuation, two actuations b.i.d.) compared to FP/SAL (500/50 µg/actuation, one inhalation b.i.d.). A cost-minimisation approach is consistent with the clinical claim.
- 6.31 The submission also calculated the equi-effective doses for the individual components of BEC/FOR 200/6 µg and four other high dose ICS/LABA FDCs currently listed on the PBS (see Table 2). A comparison of BEC/FOR 200/6 µg with medium dose ICS/LABA/LAMA therapy (MF/IND/GLY 68/114/46 µg) was added during the evaluation. Other than BEC 200 µg and FOR 6 µg (the individual components of BEC/FOR 200/6 µg FDC), the submission did not consider the cost of high dose ICS and LABA medicines provided separately. This is reasonable since it is unlikely that a patient requiring high dose ICS + LABA therapy would use two separate cannisters when multiple FDC products are available.
- 6.32 The elements used to calculate equi-effective doses are presented in the table below.

Table 9: Elements used to calculate the equi-effective dose

Treatment	Dose/Day	Pack size	Days per pack	Treatment regimen
Main comparison				
BEC/FOR (200/6 µg)	Two actuations twice daily	120 doses	30	Chronic
FP/SAL (500/50 µg)	One inhalation twice daily	60 doses	30	
FP/SAL (250/25 µg)	Two inhalations twice daily	120 doses	30	
Additional comparisons				
BEC (100 µg) + FOR (6 µg)	BEC: Four actuations twice daily	200 doses	25	Chronic
	FOR: Two actuations twice daily	60 doses	15	
MF/IND (260/125 µg)	One inhalation daily	30 doses	30	
FP/FOR (250/10 µg)	Two actuations twice daily	120 doses	30	
FF/VI (200/25 µg)	One inhalation daily	30 doses	30	
BUD/FOR (400/12 µg)	Two inhalations twice daily	2 x 60 doses	30	
BUD/FOR (200/6 µg)	Four inhalations twice daily	2 x 120 doses	30	
<i>MF/IND/GLY (68/114/46 µg)</i>	<i>One inhalation daily</i>	<i>30 doses</i>	<i>30</i>	

Source: Tables 66 & 67, pp108 & 112 of the submission; MF/IND/GLY TGA product information. Italicised text added during the evaluation. BEC = beclometasone dipropionate; BUD = budesonide; FF = fluticasone furoate; FOR = formoterol fumarate; FP = fluticasone propionate; GLY = glycopyrronium; IND = indacaterol; MF = mometasone fumarate; SAL = salmeterol; TGA = Therapeutic Goods Administration; VI = vilanterol.

- 6.33 The proposed equi-effective doses for BEC/FOR and FP/SAL were consistent with the doses and treatment regimens BEC/FOR 200/6 µg and FP/SAL 500/50 µg in the CT-01 trial and the relevant TGA product information. The proposed equi-effective doses for the additional comparisons were consistent with the relevant TGA product information. The submission conducted the cost-minimisation analysis based on the indicative prices for FP/SAL (500/50 µg and 250/25 µg) following the proposed April 2022 price disclosure reductions.
- 6.34 The prices of FP/SAL (500/50µg and 250/25µg) were not reduced in the April 2022 price disclosure cycle. Therefore, the lowest cost alternative therapies for BEC/FOR

(200/6 µg) at the time of PBAC consideration were MF/IND (260/125 µg, PBS item 12279G) and FP/FOR (250/10 µg, PBS item 10008R).

- 6.35 The cost-minimisation analysis was revised during the evaluation to equalise the cost of BEC/FOR (200/6 µg) to MF/IND (260/125 µg) and FP/FOR (250/10 µg) at AEMP per 30 days. The Pre-Sub-Committee Response (PSCR) requested that the AEMP be revised to \$45.19 to be equivalent to the current lowest cost alternative therapies MF/IND and FP/FOR. The results of the revised cost-minimisation analysis are presented in the table below. The PBAC considered the revised cost-minimisation comparison to the lowest cost-comparator to be appropriate.

Table 10: Results of the cost-minimisation analysis based on lowest cost alternative therapies (MF/IND and FP/FOR)

Component	BEC/FOR (200/6 µg)	MF/IND (260/125 µg)	FP/FOR (250/10 µg)
PBS items	N/A	12279G	10008R
Actuations per day	4	1	4
Actuations per inhaler/pack	120	30	120
Days per pack	30	30	30
AEMP/pack	\$45.19	\$45.19	\$45.19
Packs per year	12.175	12.175	12.175
Cost per year (\$)	\$550.19	\$550.19	\$550.19
Difference in cost per year vs. BEC/FOR	N/A	\$0	\$0

Source: Table 67, pp112-113 of the submission. Cost-minimisation analysis revised during the evaluation based on information provided in the submission. Cost of BEC/FOR, cost per year, difference in cost per year calculated during the evaluation.

AEMP = approved ex-manufacturer price; BEC = beclometasone dipropionate; FOR = formoterol fumarate; FP = fluticasone propionate; IND = indacaterol; MF = mometasone fumarate; N/A = not applicable; PBS = Pharmaceutical Benefits Scheme.

Drug cost/patient/course

- 6.36 The estimated cost of the lowest cost alternative therapies, MF/IND 260/125 µg and FP/FOR 250/10 µg (AEMP = \$45.19) was \$550.19. Based on the current lowest cost alternative therapies (AEMP = \$45.19), the annual cost of BEC/FOR 200/6 µg would be \$550.19.

Estimated PBS usage & financial implications

- 6.37 This submission was not considered by DUSC. The submission used a market share approach to estimate the utilisation and financial impacts associated with the PBS listing of BEC/FOR 200/6 µg for asthma. This approach is reasonable. The key inputs used in the financial estimates from the submission are presented in the table below.

Table 11: Key inputs for financial estimates

Data	Value	Source	Comment
Market size			
Scripts in current market (high dose ICS/LABA)	2,633,950	Medicare Statistics PBS item reports for 8432T, 8519J, 12279G, 10008R, 11129R, 8750M, 11301T, 10018G, 12082X (Jan-Dec '21)	This is reasonable
Current high dose ICS/LABA market share	FP/SAL: 48.86% MF/IND: 0.02% FP/FOR: 3.98%	Medicare Statistics PBS item reports for 8432T, 8519J, 12279G, 10008R, 11129R,	This is reasonable

Public Summary Document – July 2022 PBAC Meeting

Data	Value	Source	Comment
	FF/VI: 17.08% BUD/FOR: 30.07%	8750M, 11301T, 10018G, 12082X (Jan-Dec '21)	
Proportion of high dose ICS/LABA scripts attributable to asthma	80%	10% PBS data analysis (All asthma % Rx)	Data analysis based on high dose ICS/LABA medications only (not all asthma Rx). Assumed constant 80% in all calendar years. 10% PBS dataset provided shows an average of 79% 2018-2021 but a steady increase in the proportion of scripts attributable to asthma overall (64% in 2006 to 83% in 2021).
Market growth	Yr 1: 1.00% Yr 2: 1.00% Yr 3: 1.00% Yr 4: 1.00% Yr 5: 0.75% Yr 6: 0.50%	10% PBS data analysis (All asthma % Rx)	Data analysis based on high dose ICS/LABA medications only (not all asthma Rx). Years 1 to 4 based on 1.1% average market growth 2018-2021. No justification for declining market growth in Years 5 & 6. Two anomalies and two calculation errors identified in the PBS 10% dataset; however, they are unlikely to have a significant effect on the growth estimates. ^{a b}
Treatment utilisation			
Uptake rate	Yr 1: █████% Yr 2: █████% Yr 3: █████% Yr 4: █████% Yr 5: █████% Yr 6: █████%	Uptake of FP/FOR (PBS item 10008R) 2016-2021 using Medicare Statistics PBS item reports for 8432T, 8519J, 12279G, 10008R, 11129R, 8750M, 11301T, 10018G, 12082X (Jan '14 – Dec '21)	Based on the observed uptake of high dose FP/FOR. Lower and upper sensitivity analyses were conducted by halving the uptake estimate and applying the observed uptake for high dose FF/VI, respectively. Base case and sensitivity analyses are appropriate.
Scripts dispensed	Yr 1: █████ Yr 2: █████ Yr 3: █████ Yr 4: █████ Yr 5: █████ Yr 6: █████	2021 market size * market growth * proportion of market attributable to asthma * uptake rate	This calculation method is appropriate.
Costs			
BEC/FOR (200/6 µg)	\$60.67	Requested price, DPMQ	This is consistent with the cost-minimised price of the current lowest cost alternative therapy DPMQ (MF/IND and FP/FOR) which was accepted by the PSCR.
Patient copayment	PBS: \$17.98 RPBS: \$4.24	Average copayment calculated based on PBS item reports for 8432T, 8519J, 12279G, 10008R, 11129R, 8750M, 11301T, 10018G, 12082X (Jan-Dec '21)	This is reasonable

Source: Tables 70-74, pp117-120 of the submission; pp118 & 124 of the submission.

BEC = beclometasone dipropionate; BUD = budesonide; DPMQ = dispensed price for maximum quantity; FF = fluticasone furoate; FOR = formoterol fumarate; FP = fluticasone propionate; ICS = inhaled corticosteroid; IND = indacaterol; LABA = long-acting beta agonist; MBS = Medicare Benefits Schedule; MF = mometasone fumarate; PBS = Pharmaceutical Benefits Scheme; PSCR = Pre-Sub-Committee Response; RPBS = Repatriation Pharmaceutical Benefits Scheme; SAL = salmeterol; VI = vilanterol.

Public Summary Document – July 2022 PBAC Meeting

^a Anomalies in PBS dataset: (1) market share (indication) algorithm does not always reflect PBS restriction, e.g., FF/VI is only indicated for asthma (i.e., asthma indication should be 100% of market share) but algorithm predicts 61-78% sales for asthma indication; (2) sales recorded for medicines before they were PBS listed (e.g., FF/VI (PBS item 11129R) was listed in 2017 but PBS 10% data shows 230,286 units sold in 2014-2016.

^b calculation (cell reference) errors: (1) # asthma units for FF/VI references market share algorithm for FP/SAL (row 22) instead of FF/VI (row 7); (2) # asthma units for BUD/FOR 400/12 references market share algorithm for FP/SAL (row 22) instead of BUD/FOR 400/12 (row 10).

The redacted values correspond to the following ranges:

¹10,000 to < 20,000

²40,000 to < 50,000

³60,000 to < 70,000

⁴70,000 to < 80,000

⁵80,000 to < 90,000

6.38 The submission presented estimated financial implications for the listing of BEC/FOR 200/6 µg based on the price cost minimised to FP/SAL (500/50µg and 250/25 µg) at the indicative April 2022 price (DPMQ = \$56.01). The submission also presented two supplementary price analyses:

- Supplementary price analysis #1: no price reduction for FP/SAL (500/50µg and 250/25 µg, DPMQ = \$62.38); BEC/FOR 200/6 µg cost minimised to the current lowest cost alternative therapies (MF/IND 260/125 µg & FP/FOR 250/10 µg, DPMQ = \$60.67),
- Supplementary price analysis #2: no price reduction for FP/SAL (500/50µg and 250/25 µg, DPMQ = \$62.38); BEC/FOR 200/6 µg cost minimised to the current market leader (FP/SAL 500/50µg and 250/25 µg, DPMQ = \$62.38).

6.39 Since FP/SAL (500/50 µg and 250/25 µg) did not undergo a price reduction in April 2022, supplementary price analysis #1 more accurately reflects the expected cost of listing BEC/FOR 200/6 µg on the PBS. The PSCR agreed with this analysis. Therefore, the estimated financial implications for the listing of BEC/FOR 200/6 µg based on the price cost minimised to MF/IND 260/125 µg & FP/FOR 250/10 µg (DPMQ = \$60.67) and a DPMQ of \$62.38 for FP/SAL (500/50µg and 250/25 µg) (submission supplementary price analysis #1) are presented in the table below.

Table 12: Estimated use and financial implications – submission – supplementary price analysis #1^a

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed ^b	¹	²	³	⁴	⁵	⁵
Estimated financial implications of BEC/FOR						
Cost to PBS/RPBS less copayments (\$)	⁶	⁶	⁶	⁶	⁶	⁶
Estimated financial implications for FP/SAL, MF/IND, FP/FOR, FF/VI, BUD/FOR						
Cost to PBS/RPBS less copayments (\$)	⁷	⁷	⁷	⁷	⁷	⁷
Net financial implications						
Net cost to PBS/RPBS (\$)	⁷	⁷	⁷	⁷	⁷	⁷
Net cost to MBS (\$)	⁶	⁶	⁶	⁶	⁶	⁶
Net cost to Government (\$)	⁷	⁷	⁷	⁷	⁷	⁷

Source: Tables 74, 76, 78 & 81, pp120-121, 123 & 125 of the submission.

BEC = beclometasone dipropionate; BUD = budesonide; DPMQ = dispensed price for maximum quantity; FF = fluticasone furoate; FOR = formoterol fumarate; FP = fluticasone propionate; IND = indacaterol; MBS = Medicare Benefits Schedule; MF = mometasone fumarate; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; SAL = salmeterol; VI = vilanterol.

^a DPMQ of BEC/FOR (200/6 µg) = MF/IND 260/125 µg & FP/FOR 250/10 µg = \$60.67; DPMQ of FP/SAL (500/50µg and 250/25µg) = \$62.38

^b Assuming 12.175 packs per year as estimated by the submission.

The redacted values correspond to the following ranges:

¹ 10,000 to < 20,000

² 40,000 to < 50,000

³ 60,000 to < 70,000

⁴ 70,000 to < 80,000

⁵ 80,000 to < 90,000

⁶ \$0 to < \$10 million

⁷ net cost save

6.40 In supplementary price analysis #1 (assuming no price reduction to FP/SAL and cost-minimising BEC/FOR to MF/IND and FP/FOR), the total cost to the PBS/RPBS of listing BEC/FOR 200/6 µg was estimated to be a saving of net cost saving in Year 6, and a total saving of net cost saving in the first 6 years of listing. The cost savings were associated with decreased utilisation of more expensive ICS/LABA combination therapies.

Quality Use of Medicines

6.41 The submission stated that education materials setting out the appropriate dosing of BEC/FOR 200/6 µg would be available and that a medical team would visit all treating centres to educate physicians and nurse practitioners on the approved dosing schedules.

6.42 The quality use of medicines plan proposed did not consider 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. The PBAC noted the already extensive range of high-dose ICS/LABA medicines on the PBS and noted the risk for consumers in terms of confusion regarding correct inhaler use, particularly when switching between alternatives. Therefore, the PBAC advised the sponsor should consider partnering with a consumer or other organisation such as NPS MedicineWise or the National Asthma Council to ensure that instructions on inhaler device use are clear and readily accessible. Similarly, health professional education beyond appropriate dosing may be required to ensure that health professionals are adequately skilled to support consumers in device use.

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

7 PBAC Outcome

7.1 The PBAC recommended an Authority Required (STREAMLINED) listing for Fostair® 200/6 µg metered dose inhaler (MDI), a fixed dose combination (FDC) of beclometasone (BEC), an inhaled corticosteroid (ICS) with formoterol (FOR), a long-acting beta agonist (LABA) as maintenance treatment of asthma.

- 7.2 The PBAC considered the claim of non-inferior effectiveness and safety to the FDC of fluticasone propionate with salmeterol (FP/SAL 500/50 µg, two inhalations daily and 250/25 µg, four actuations daily) was reasonable. However, the PBAC considered for purposes of satisfying Section 101(3B) of the *National Health Act 1953*, any high dose ICS/LABA FDCs are relevant alternative therapies. The PBAC's recommendation for listing was therefore based on, among other matters, its assessment that the cost-effectiveness for BEC/FOR 200/6 µg would be acceptable if it was cost-minimised against the least costly high dose ICS/LABA FDC.
- 7.3 The PBAC noted the input from Asthma Australia which supported the listing of BEC/FOR 200/6 µg for the maintenance treatment of asthma.
- 7.4 The PBAC advised the nominated main comparator FP/SAL 500/50 µg was appropriate based on the clinical evidence provided by the head-to-head randomised trial. In addition, the PBAC also considered all high dose ICS/LABA FDCs currently listed for asthma were appropriate alternative therapies (see Table 2).
- 7.5 The PBAC considered the claim of non-inferior effectiveness and safety was supported by the results of CT-01, a head-to-head randomised trial comparing BEC/FOR 200/6 µg as maintenance treatment to FP/SAL 500/50 µg in severe persistent asthma patients. The PBAC accepted non-inferiority based on the primary outcome of change from baseline to the end of the treatment in pre-dose morning FEV1 at 24 weeks, based on a pre-specified non-inferiority margin of 0.2 L in the CT-01 trial. Additionally, there were no statistically significant differences between BEC/FOR 200/6 µg and FP/SAL 500/50 µg in any of the secondary outcomes reported in the CT-01 trial, and the differences between the treatments appeared small. The PBAC also noted the number and proportion of patients experiencing adverse events were similar between the BEC/FOR 200/6 µg and FP/SAL 500/50 µg treatment arms. The PBAC considered it reasonable to extend the non-inferiority claim to other high-dose ICS/LABA listings on the PBS.
- 7.6 The PBAC noted that the submission presented a cost-minimisation analysis between BEC/FOR 200/6 µg and FP/SAL. However, the PBAC considered the cost of BEC/FOR 200/6 µg should be no greater than the least costly high dose ICS/LABA FDC. The PBAC accepted the equi-effective doses outlined in Table 9.
- 7.7 The PBAC considered the estimates provided in the submission where BEC/FOR 200/6 µg was cost minimised to the current lowest cost alternative therapies (MF/IND 260/125 µg & FP/FOR 250/10 µg) (supplementary analysis #1) were reasonable and noted that the cost savings presented were associated with decreased utilisation of more expensive ICS/LABA FDCs.
- 7.8 The PBAC recommended that under Section 101(3BA) of the *National Health Act, 1953* BEC/FOR 200/6 µg 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.

- 7.9 The PBAC advised that BEC/FOR 200/6 µg is suitable for prescribing by nurse practitioners.
- 7.10 The PBAC recommended that the Early Supply Rule should not apply.
- 7.11 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because BEC/FOR 200/6 µg 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 2022* 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 Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
BECLOMETASONE + FORMOTEROL (EFORMOTEROL)					
beclometasone dipropionate 200 microgram/actuation + formoterol (eformoterol) fumarate dihydrate 6 microgram/actuation inhalation, 120 actuations	NEW	1	1	5	Fostair 200/6
Restriction Summary [11014] / Treatment of Concept: [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) /existing code 11057				
9277	Indication: Asthma				
9539	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.				
28690	Administrative Advice: This pharmaceutical benefit is not for the treatment of chronic obstructive pulmonary disease (COPD).				
22302	Administrative Advice: The patient must not be on a concomitant single agent long-acting-beta-2-agonist (LABA).				
21822	Administrative Advice: A LABA includes olodaterol, indacaterol, salmeterol, formoterol or vilanterol.				
21825	Administrative Advice: Adherence to current treatment and device (inhaler) technique should be reviewed at each clinical visit. and before "stepping up" a patient's medication regimen.				
26570	Administrative Advice: This product is not PBS subsidised for use as 'maintenance and reliever' therapy.				
26584	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.