

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

1 Purpose of submission

- 1.1 The Category 2 submission requested an Authority Required (STREAMLINED) listing of Fostair[®], a fixed-dose combination (FDC) of the inhaled corticosteroid (ICS) beclometasone dipropionate (BEC) (100 µg) with the long-acting β2-agonist (LABA) formoterol fumarate dihydrate (FOR) (6 µg) delivered via a pressurised metered dose inhaler (pMDI) for the treatment of chronic obstructive pulmonary disease (COPD).
- 1.2 Listing was requested on the basis of a cost-minimisation analysis versus the FDC of fluticasone propionate (FP) 250 µg with salmeterol (SAL) 25 µg (Table 1). The submission also nominated the FDC of budesonide (BUD) 400 µg with FOR 12 µg as a secondary comparator.

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

Component	Description
Population	Adults with severe COPD (FEV1 less than 50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators
Intervention	BEC/FOR (100/6 µg per actuation). Delivered dose (ex-actuator) contains 84.6 µg BEC and 5.0 µg FOR
Comparator	FP/SAL (250/25 µg per actuation)
Outcomes	<p>Primary:</p> <ul style="list-style-type: none"> Transition Dyspnoea Index (TDI) score at week 12 Change from pre-dose in FEV1 after drug inhalation during the morning of baseline visit (AUC_{0-30min}). <p>Secondary:</p> <ul style="list-style-type: none"> Pulmonary function tests at baseline and week 12 COPD symptom score at baseline and week 12 COPD exacerbation occurrence St. George's Respiratory Questionnaire (SGRQ) at baseline and week 12 Six-minute walking test (6MWT) at baseline and week 12
Clinical claim	BEC/FOR 100/6 µg is non-inferior in terms of efficacy and safety when compared to FP/SAL 250/25 µg for the treatment of COPD

Abbreviations: AUC = Area under the curve; BEC= Beclometasone dipropionate; FOR= Formoterol fumarate dehydrate; FP= Fluticasone propionate; SAL= Salmeterol; COPD= Chronic obstructive pulmonary disease; FEV1= Forced expiratory volume; SGRQ= St. George's respiratory questionnaire; 6MWT= Six-minute walking test; TDI= transition dyspnoea index.

Source: Based on Table 10, p3 of the submission.

2 Background

Registration status

- 2.1 BEC/FOR was approved by the TGA on 20th January 2020 for an asthma population and for symptomatic treatment of adults with severe COPD. The TGA indication for BEC/FOR for COPD is: ‘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’.
- 2.2 BEC/FOR was officially registered on the Australian Register of Therapeutic Goods on 12th February 2020 (ARTG ID: 310360). BEC/FOR has been approved in 73 countries for both asthma and COPD.

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

3 Requested listing

- 3.1 The requested restriction is presented below. 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 cod	Max. qty packs	Max. qty units	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
BECLOMETASONE with FORMOTEROL beclometasone dipropionate 100 microgram/actuation + formoterol (eformoterol) fumarate dihydrate 6 microgram/actuation inhalation, 120 actuations	12183F	1	1	5	\$	Fostair®	Chiesi Australia Pty Ltd

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required - Streamlined
Condition: Chronic obstructive pulmonary disease (COPD)
Indication: Chronic obstructive pulmonary disease (COPD)
Treatment Phase: initial and continuing
Clinical criteria: Patient must have significant symptoms despite regular <i>long-acting beta-2 agonist</i> bronchodilator therapy
AND
Clinical criteria: Patient must have experienced at least one severe COPD exacerbation, which required hospitalisation, or two or more moderate exacerbations in the previous 12 months <i>prior to commencing treatment for COPD</i>
Administrative Advice: This product is not indicated for the initiation of bronchodilator therapy in COPD.

	Administrative Advice: The treatment must not be used in combination with LABA monotherapy or LAMA/LABA combination therapy.
	Administrative Advice: A LAMA/LABA includes acclidinium/formoterol, glycopyrronium/indacaterol, tiotropium/olodaterol, or umeclidinium/vilanterol.
	Administrative Advice: Diagnosis of COPD should include measurement of airflow obstruction using spirometry, with confirmation of post-bronchodilator airflow obstruction.

- 3.2 The requested PBS list price of BEC/FOR in this submission was calculated based on prices separately in asthma and in COPD, weighted by the utilisation in the two indications. The weighted average ex-manufacturer price (AEMP) requested was \$~~1~~, with a corresponding DPMQ of \$~~1~~.
- 3.3 The clinical criteria and administrative advice were consistent with the existing COPD PBS restriction of the main comparator FP/SAL (PBS item 8519J). The PBAC noted the TGA indication for BEC/FOR includes reference to ‘significant symptoms despite regular therapy with long-acting bronchodilators’ and considered the clinical criteria should be updated accordingly.
- 3.4 The proposed restriction states that patients must have had at least one severe COPD exacerbation, which required hospitalisation, or two or more moderate exacerbations in the previous 12 months. However, at baseline patients in the FUTURE trial had a mean of only 0.4 exacerbations in the previous 12 months (see paragraph 6.11). It is unclear how many of these COPD exacerbations were hospitalised.

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

4 Population and disease

- 4.1 COPD is a serious, progressive, and disabling condition, and one of the two most common causes of adult airflow obstruction along with asthma. COPD is characterised by airflow obstruction that cannot be easily reversed with medication. Airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung caused by significant exposure to noxious particles or gases.
- 4.2 According to self-reported data in the 2018-2019 National Health Survey, COPD prevalence was 4.8% of Australians over 45 years of age. The prevalence of COPD increases with age, mostly occurring in people aged 45 and over. COPD was the second leading cause of total disease burden for men aged 65–74 and 75–84 and the leading cause for women aged 65–74 (AIHW¹).
- 4.3 The submission proposed that BEC/FOR would be an alternative to currently listed ICS/LABAs FDCs for COPD. Existing ICS/LABA FDCs are generally used to treat adults

¹ <https://www.aihw.gov.au/reports/asthma-other-chronic-respiratory-conditions/copd-chronic-obstructive-pulmonary-disease/contents/deaths>

with severe COPD (FEV1 less than 50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with a LABA.

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

5 Comparator

- 5.1 The submission nominated FP/SAL as the main comparator. The submission argued that this FDC is the current market leader in the symptomatic treatment of severe COPD in Australia. As it is the most used treatment for COPD, it would therefore be the treatment most likely to be displaced in practice should BEC/FOR be listed.
- 5.2 The submission stated that the individual components of BEC/FOR are PBS-listed only for asthma, not for COPD and hence it was not appropriate to consider the concurrent administration of the components as a comparator. A number of single component ICS inhalers have an unrestricted listing on the PBS but none are TGA registered for COPD.
- 5.3 The submission also noted that there are other ICS/LABA FDCs listed on the PBS for COPD that could be considered potential comparators (Table 2). The submission stated that these are less relevant, as their share of the COPD market is smaller than that of FP/SAL and that only FP/SAL provides the same duration of treatment (30 days per pack). The ESC considered the other ICS/LABA combinations listed for COPD outlined in Table 2 were relevant alternatives.

Table 2: ICS/LABA inhalers PBS-listed for COPD that may be considered alternatives to the intervention (BEC/FOR)

PBS Code	Brand(s)	Strength and Form	Days per inhaler	Included in Clinical comparison	Considered in Economics section	Included in utilisation and financial estimates
8519J	Seretide 250/25; Cipla 250/25; Pavtide; SalplusF Inhaler 250/25; Seroflo 250/25	Fluticasone 250 µg /actuation + salmeterol 25 µg /actuation inhalation, 120 actuations	30	No	Yes	Yes
8432T	Seretide Accuhaler 500/50; Pavtide Accuhaler 500/50	Fluticasone 500 µg /actuation + salmeterol 50 µg /actuation powder for inhalation, 60 actuations	30	Yes	Yes	Yes
10018G	Symbicort Rapihaler 200/6	Budesonide 200 µg /actuation + formoterol fumarate dihydrate 6 µg /actuation inhalation, 120 actuations	60	No ^a	Yes	Yes
8750M	Symbicort Turbuhaler 400/12	Budesonide 400 µg /actuation + formoterol fumarate dihydrate 12 µg /actuation powder for inhalation, 2 x 60 actuations	60	No	Yes	Yes

PBS Code	Brand(s)	Strength and Form	Days per inhaler	Included in Clinical comparison	Considered in Economics section	Included in utilisation and financial estimates
11301T	BiResp Spiromax, DuoResp Spiromax	Budesonide 400 µg /actuation + formoterol fumarate dihydrate 12 µg /actuation powder for inhalation, 2 x 60 actuations	60	No	Yes	Yes
11124L	Breo Ellipta 100/25	Fluticasone fumarate 100 µg /actuation + vilanterol 25 µg /actuation powder for inhalation, 30 actuations	30	No	No	Yes

^aSymbicort Turbuhaler 200 µg/6 µg was used in the Calverley et al (2010) trial but is not PBS listed for COPD.
Source: Based on Table 66, p95 of the submission.

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 the Lung Foundation of Australia, which supported the listing of BEC/FOR in COPD, highlighting it would provide an additional ICS/LABA treatment option for patients.

Clinical trials

6.3 The submission was based on one head-to-head randomised controlled trial (RCT), FUTURE, comparing BEC/FOR to FP/SAL and one head-to-head RCT, Calverley et al. (2010), comparing BEC/FOR vs. BUD/FOR vs. FOR.

6.4 The clinical claim for BEC/FOR vs. FP/SAL was based on the subgroup of patients in FUTURE with FEV1 < 50%. As the FUTURE trial included patients with moderate-severe COPD (FEV1 less than 60% predicted normal), which is outside of the TGA indication for FOSTAIR, results from the ITT population are presented as well as results from patients in the severe COPD population only (FEV1 less than 50% predicted normal).

6.5 The FORWARD trial was included as a supplementary study as it consisted of a comparison of BEC/FOR against a LABA (formoterol) in the treatment of COPD. However, formoterol is not listed on the PBS for the treatment of COPD and as such this comparison was not detailed in the evaluation.

6.6 Details of the trials are provided in Table 3.

Table 3: FUTURE and Calverley et al. (2010) trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Future Trial	<p>A 12-week, multicentre, multinational, randomized, double-blind, double-dummy, 2-arm parallel group study comparing the efficacy and safety of Foster 100/6 (beclomethasone dipropionate 100 µg plus formoterol 6 µg/actuation), 2 puffs b.i.d., versus FP/SAL 500/50 (fluticasone 500 µg plus salmeterol 50 µg/actuation), 1 inhalation b.i.d., in patients with Chronic Obstructive Pulmonary Disease</p> <p>Singh, D., Nicolini, G., Bindi, E. <i>et al.</i> Extrafine Beclomethasone/formoterol compared to Fluticasone/salmeterol Combination Therapy in COPD.</p>	<p>12 March 2014</p> <p>BMC Pulmonary Medicine 2014; 14(43)</p>
Calverley et al., (2010)	<p>A 48-week, double blind, double dummy, randomised, multinational, multicentre, 3-arm parallel group clinical study of “fixed combination” Beclomethasone dipropionate plus Formoterol fumarate administered via pMDI with HFA-134a propellant (CHF 1535) versus “fixed combination” Budesonide plus Formoterol DPI (BUD/FOR Turbohaler, AstraZeneca) versus Formoterol DPI (Oxis Turbohaler, AstraZeneca) in patients with stable severe chronic obstructive pulmonary disease (COPD)</p> <p>Calverley, P.M.A., Kuna, P., Monsó, E., Costantini, M., Petruzzelli, S., Sergio, F., Varoli, G., Papi, A. and Brusasco, V., 2010. Beclomethasone/formoterol in the management of COPD: a randomised controlled trial</p>	<p>20 October 2010</p> <p>Respiratory Medicine 2010 104(12): 1858-1868.</p>

Abbreviations: COPD = Chronic obstructive pulmonary disease; DPI=Dry powder inhaler; BUD= Budesonide; FF=Fluticasone fumarate; FOR=Formoterol; FP=Fluticasone propionate; SAL=Salmeterol.

Source: Table 2.2.6, p29 of the submission.

6.7 The key features of the two RCTs are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N Treatment arms	Design/ duration	Risk of bias	Patient population	Outcomes
FUTURE	419 (ITT), 241 (FEV1<50%) subgroup BEC/FOR 100/6 µg 2 inhalations twice daily (pMDI) FP/SAL 500/50 µg 1 inhalation twice daily (accuhaler)	R, DB 12 weeks + 2-week run-in	Low	<ul style="list-style-type: none"> • ≥40 years • Regular bronchodilator use in the previous 2 months • ≥10 pack-years smoking history • Moderate-severe COPD diagnosis • FEV1 <60% of predicted normal, post-bronchodilator • FEV1/FVC < 0.7, post-bronchodilator • Increase in FEV1 ≥ 5% following 400µg salbutamol • BDI focal score ≤ 10 • ≤ one COPD exacerbation treated with antibiotics or systemic corticosteroids in the previous 12 months. 	<p>Primary</p> <ul style="list-style-type: none"> • TDI score at week 12 • Change in FEV1 after drug inhalation at baseline <p>Secondary</p> <ul style="list-style-type: none"> • Pulmonary function tests at baseline and week 12 • COPD symptom score at baseline and week 12 • COPD exacerbation occurrence • SGRQ at baseline and week 12 • 6MWT at baseline and week 12 • Use of rescue medication
Calverley et al. (2010)	703 BEC/FOR 100/6 µg 2 inhalations twice daily (pMDI) BUD/FOR 200/6 µg 2 inhalations twice daily (turbuhaler) FOR 12 µg 1 inhalation twice daily (turbuhaler)	R, DB 48 weeks + 4-week run-in	Low	<ul style="list-style-type: none"> • ≥40 years • clinical diagnosis of COPD (GOLD guidelines) • >20 pack-years smoking history • FEV1 ≥ 30% and < 50% predicted normal, post-bronchodilator • FEV1/FVC ≤ 0.7, post-bronchodilator • COPD symptoms for ≥ 2 years • ≥ 1 exacerbation requiring medical intervention within 2-12 months prior to screening 	<p>Primary</p> <ul style="list-style-type: none"> • Change in pre-dose FEV1 from baseline to 48 weeks • No. of COPD exacerbations during the 48-week period <p>Secondary</p> <ul style="list-style-type: none"> • Pulmonary function tests at baseline to week 48 • Dyspnoea index score at baseline to week 48 • SGRQ at baseline to week 48 • 6MWT at baseline to week 48 • BODE index score • COPD symptom score • Use of rescue medication

Abbreviations: R= Randomised control trial; DB= Double blinded; BEC= Beclometasone dipropionate; BUD= Budesonide; FOR= Formoterol fumarate dehydrate; FP= Fluticasone propionate; SAL= Salmeterol. ADR= Adverse Drug Reaction; COPD= Chronic Obstructive Pulmonary Disease; FEV1= Forced Expiratory Volume; BDI= Baseline Dyspnoea Index; SGRQ=St. George’s respiratory questionnaire; 6MWT= 6-minute walking test; BODE= Body-mass index, airflow obstruction, dyspnoea and exercise; SD= Standard deviation.
Source: Table 24 and Table p 35 of submission.

6.8 The primary objective of the FUTURE trial was to demonstrate the superiority of BEC/FOR versus FP/SAL in terms of lung function $AUC_{(0-30min)}$ standardised by time of change from pre-dose in FEV1 after drug inhalation in the morning of day 1 (baseline), and the equivalence between BEC/FOR and FP/SAL in terms of the Transition Dyspnoea Index (TDI) score at day 84 in patients with COPD. The change from pre-dose in FEV1 after drug inhalation outcome was intended to show the faster onset of action of BEC/FOR over FP/SAL. As this outcome is not a measure of long-term patient improvement there is no MCID for this measure. To assess long-term patient outcomes, the submission stated the FUTURE trial used other primary and secondary endpoints, for example, the TDI score (primary outcome) and change in pre-dose morning FEV1 from baseline to week 12 (secondary endpoint), for which there are established MCIDs (see paragraph 6.13).

- 6.9 The primary objective of the Calverley et al. (2010) trial was to demonstrate that BEC/FOR was non-inferior to BUD/FOR in terms of lung function (change in pre-dose morning FEV1 at baseline to 48 weeks) and superior to FOR alone in terms of exacerbation rates in patients with severe COPD.
- 6.10 Whilst the evidence for BEC/FOR versus FP/SAL was provided by a double-blind RCT (FUTURE), the 12 week follow-up time of the trial was shorter than the trial of Calverley et al. (2010). The duration of the FUTURE trial may be too short to provide an accurate estimate of the effect of treatment on the key clinical outcomes. For example, the treatment effects for change in FEV1 from baseline in the Calverley et al. (2010) trial varied according to follow up, from 12 to 48 weeks. The Pre-Sub-Committee Response (PSCR) noted that PBAC had previously accepted non inferiority for fluticasone furoate plus vilanterol based on a 12-week study (paragraph 6.9, fluticasone furoate plus vilanterol Public Summary Document (PSD), July 2014 PBAC Meeting).
- 6.11 The FUTURE trial characteristics were generally consistent with the requested restriction and the Australian population, with the exception of the history of previous exacerbations. The proposed restriction states that patients must have had at least one severe COPD exacerbation, which required hospitalisation, or two or more moderate exacerbations in the previous 12 months. However, FUTURE trial inclusion criteria required patients to have a history of less than or equal to one COPD exacerbation treated with antibiotics or systemic corticosteroids in the previous 12 months. At baseline, patients in the FUTURE trial had a mean of only 0.4 exacerbations in the previous 12 months. It is unclear how many of these exacerbations led to hospitalisations. The inclusion criterion for COPD exacerbations in the Calverley et al. (2010) trial was different than in the FUTURE trial. The inclusion criterion (at least 1 exacerbation requiring medical intervention) of the Calverley et al. (2010) is more consistent with the proposed PBS restriction.
- 6.12 The submission appropriately presented the results of many clinical outcomes. The rate of exacerbation and the change in FEV1 were key outcomes, as established in previous PBAC assessments in COPD. In 2014, the PBAC considered lung function (i.e. FEV1), frequency of exacerbations and hospitalisations as being patient relevant outcomes in COPD (paragraph 6.8, FF/VI Breo Ellipta, PSD March 2014 PBAC meeting). In the recent assessment of BEC/FOR/GLY, the claim of non-inferiority was based solely on rates of exacerbation (BEC/FOR/GLY Trimbrow, PSD November 2020 PBAC meeting). In the recent assessment of BUD/GLY/FOR, for COPD, the ESC considered the clinical claim based on the rates of moderate or severe exacerbations and change in FEV1, SGRQ score and rescue medication (paragraph 6.22, BUD/GLY/FOR Breztri, PSD July 2021 PBAC meeting).
- 6.13 While no MCID was proposed for change from pre-dose in FEV1 after drug inhalation (see paragraph 6.8) in the FUTURE trial, an MCID of ≥ 100 ml was proposed for change in pre-dose morning FEV1 from baseline to 48 weeks for the Calverley et al. (2010) trial. The PBAC previously considered that an increase in FEV1 of 100 ml (from baseline

to end of the trial at 52 weeks) was likely to be clinically meaningful for moderate to severe COPD for FF/UMEC/VI (paragraph 6.21, FF/UMEC/VI Trelegy Ellipta, PSD December 2017 PBAC meeting). Thus, an MCID of ≥ 100 ml is likely to be appropriate. The submission did not nominate MCIDs for COPD exacerbations. This is consistent with the submission for FF/UMEC/VI (paragraph 6.21, FF/UMEC/VI PSD December 2017 PBAC meeting). An increase of ≥ 1 in TDI focal score was put forward which is consistent with the MCID nominated in the COPD-X guidelines for TDI. The MCID for the St George's Respiratory Questionnaire (SRGQ) total score was a decrease of ≥ 4 units. This is consistent with COPD-X guidelines and the MCID previously considered by the PBAC for FF/UMEC/VI (paragraph 6.21, FF/UMEC/VI Trelegy Ellipta, PSD December 2017 PBAC meeting).

- 6.14 In terms of non-inferiority, for the TDI score in the FUTURE study, the submission stated it was demonstrated if the two-sided 95% for the adjusted mean difference was entirely within the equivalence margins fixed at ± 1 . The PBAC has not previously considered a non-inferiority margin for this outcome. In the Calverley et al. (2010) trial, non-inferiority was declared if the lower limit of the two-sided 95% CI for the difference between adjusted treatment means was above the non-inferiority margin fixed at -100 ml for the change in pre-dose morning FEV1 from baseline to 48 weeks.

Comparative effectiveness

- 6.15 The key results of the FUTURE trial are presented in Table 5.

Table 5: Key efficacy outcomes reported in the FUTURE trial

Outcome	ITT population			FEV1 < 50% subgroup		
	BEC/FOR n=211 Adj. mean (95% CI)	FP/SAL n=207 Adj. mean (95% CI)	Mean differences	BEC/FOR n=119 Adj. mean (95% CI)	FP/SAL n=122 Adj. mean (95% CI)	Mean differences
Primary outcomes						
Change in pre dose FEV1 (L*30min) after drug inhalation (Standardised) ^a	0.177 (0.160, 0.194)	0.105 (0.087, 0.122)	0.073 (0.050, 0.095)	0.173 (0.152, 0.194)	0.098 (0.076, 0.119)	0.075 (0.048, 0.103)
TDI score (Week 12)	1.316 (0.865, 1.766)	1.150 (0.696, 1.604)	0.165 (-0.387, 0.718)	0.889 (0.303, 1.476)	0.950 (0.374, 1.527)	-0.061 (-0.779, 0.656)
Secondary outcomes						
Change from baseline in pre-dose FEV1 (L*30min) after drug inhalation (week 12) ^b	0.217 (0.183, 0.252)	0.136 (0.100, 0.172)	0.081 (0.036, 0.126)	0.178 (0.138, 0.218)	0.112 (0.072, 0.153)	0.066 (0.013, 0.118)
Change from baseline in pre-dose morning FEV1 (L) (week 12) ^b	0.077 (0.044, 0.110)	0.064 (0.031, 0.098)	0.013 (-0.031, 0.056)	0.037 (0.000, 0.074)	0.064 (0.026, 0.101)	-0.027 (-0.076, 0.023)
No. patients with COPD exacerbation ^a	6 (2.8%)	4 (1.9%)	N/A	5 (4.2%)	3 (2.5%)	N/A
Change from baseline in total SGRQ score (Week 12)	-5.915 (-7.749, -4.081)	-3.802 (-5.703, -1.901)	-2.113 (-4.480, 0.253)	-4.611 (-6.952, -2.270)	-3.541 (-5.943, -1.139)	-1.070 (-4.121, 1.982)
Change from baseline in COPD symptom total score (Week 12) ^c	-1.209 (-1.550, -0.868)	-1.000 (-1.346, -0.654)	-0.209 (-0.660, 0.243)	-1.047 (-1.519, -0.575)	-0.793 (-1.269, -0.318)	-0.254 (-0.884, 0.377)
Change from baseline in use of rescue medication (Week 12)	-0.599 (-0.778, -0.419)	-0.629 (-0.812, -0.446)	0.030 (-0.209, 0.270)	-0.577 (-0.841, -0.313)	-0.716 (-0.981, -0.451)	0.139 (-0.215, 0.493)

Abbreviations: BEC= Beclometasone dipropionate; FOR= Formoterol fumarate dehydrate; FP= Fluticasone propionate; SAL= Salmeterol; COPD= Chronic obstructive pulmonary disease; FEV1= Forced Expiratory Volume; SGRQ= St. George's Respiratory Questionnaire; TDI= Transition dyspnoea index.

CI = confidence interval; COPD = (95% CI); FEV1 = (95% CI); SGRQ = (95% CI).

Bold means statistically significant mean difference.

^a Standardised by time of change from pre-dose in FEV1 after drug inhalation in the morning of day 1 (baseline).

^b Not standardised.

^c COPD exacerbations between date of Visit 2 and the end of the study and derived from the consumption of resources form are considered for the analysis. Percentages are calculated on the number of patients (N).

Source: Table 37, 38, 43, 47 and 50, p60-75 of the submission.

6.16 Change in pre-dose morning forced expiratory volume (FEV1) area under the curve zero to thirty minutes (standardised by time of change from pre-dose in FEV1) after drug inhalation at the baseline visit compared treatments in terms of their onset of action. The increase in FEV1 was found to be significantly higher in the BEC/FOR group compared to the FP/SAL group (adjusted mean difference 73 ml; $p = <0.001$) (Table 5). The change in this outcome was also found to be significant when measured at week 12 (Table 5). As outlined in paragraph 6.8, this outcome was intended to show the faster onset of action of BEC/FOR over FP/SAL and is not a measure of long-term patient improvement.

- 6.17 No statistically significant differences between treatment arms was identified for the other primary outcome of the FUTURE trial, TDI score. The difference between the BEC/FOR group and the FP/SAL group in the ANCOVA model and the 95% CI for the difference (-0.387 to 0.718) lay entirely within the proposed ± 1 equivalence margins.
- 6.18 No statistically significant differences were seen between BEC/FOR and FP/SAL in the remaining key secondary outcomes reported in Table 5.
- 6.19 The key results of the Calverley et al. (2010) trial are presented in Table 6.

Table 6: Key efficacy outcomes reported in the Calverley et al. (2010) trial

	BEC/FOR n=232	BUD/FOR n=242	FOR n=238	BEC/FOR vs. BUD/FOR	BEC/FOR vs. FOR
Outcome	Adjusted mean	Adjusted mean	Adjusted mean	Adjusted Mean difference (95% CI)	Adjusted mean difference (95% CI)
Primary outcomes					
Change from baseline in pre-dose FEV1 (L) (week 48)	0.077	0.080	0.026	-0.002 (-0.052) ^a	0.051 (0.001, 0.102), p= 0.046
Mean rate per patient/year COPD exacerbations	0.414 ^b	0.423 ^b	0.431 ^b	0.979 ^c (0.722, 1.326)	0.961 ^c (0.707, 1.305)
Secondary outcomes					
Mean rate per patient/year COPD exacerbations leading to hospitalisation	0.074 ^b	0.033 ^b	0.040 ^b	2.222^c (1.384, 3.567), p<0.001	1.844^c (1.173, 2.901), p=0.008
Change from baseline in dyspnoea score (Week 48)	-0.14	-0.19	-0.05	0.05 (-0.07, 0.17)	-0.09 (-0.21, 0.03)
Change from baseline in total SGRQ score (Week 48)	-3.70	-4.67	-2.84	0.98 (-1.26, 3.21)	-0.86 (-3.10, 1.39)
Change from baseline in % of symptom free days (Week 48)	2.63%	3.24%	3.82 %	-0.61 (-4.95, 3.73)	-1.18 (-5.55, 3.18)
Change from baseline in use of rescue medication (Week 48)	-0.23	-0.23	-0.11	0.02 (-0.19, 0.22)	-0.11 ^d (-0.32, 0.10)

Abbreviations: BEC= Beclometasone dipropionate; FOR= Formoterol fumarate dehydrate; FP= Fluticasone propionate; SAL= Salmeterol; FEV1= Forced Expiratory Volume; COPD= Chronic obstructive pulmonary disease; SGRQ= St. George's Respiratory Questionnaire. CI = confidence interval. COPD = 95% CI; FEV1 = 95% CI; SGRQ = 95% CI. CI = confidence interval. COPD = 95% CI; FEV1 = 95% CI; SGRQ = 95% CI.

Bold indicates statistical significance.

^a Unilateral 97.5% CI

^b Mean rate per patient/year

^c Indicates rate ratio (95% CI)

^d Table 3 of the submission presents this value as 0.11. "(should be -0.11)".

Source: Table 41, 42, 44, 46, 48 and 51. p 65-76 of the submission.

- 6.20 In the Calverley et al. (2010) trial, change in pre-dose morning FEV1 from baseline to 48 weeks did not vary significantly by treatment between BEC/FOR and BUD/FOR. However, the lower 95% confidence interval of the difference between BEC/FOR and BUD/FOR was less than 100ml, which support non-inferior effectiveness for this outcome.
- 6.21 The co-primary outcome of mean rate of COPD exacerbations per patient per year were similar across the three treatment groups. The submission did not attempt to consider whether BEC/FOR was non-inferior to BUD/FOR based on rates of

exacerbation. However, the upper 95% confidence interval of the exacerbation rate ratio for BEC/FOR versus BUD/FOR was high, at 1.33, implying that BEC/FOR may not be considered non-inferior to BUD/FOR based on this outcome.

- 6.22 BEC/FOR was not superior to FOR alone in terms of exacerbations. However, the TGA Public Assessment Report for BEC/FOR stated the reduction in exacerbations was much less than anticipated in the power calculations, thus it is likely that the study was underpowered for this outcome.
- 6.23 The rate of COPD exacerbations leading to hospitalisation was significantly higher in the BEC/FOR group (0.074 per patient/year) than in the BUD/FOR group (0.033 per patient/year; $p < 0.001$) and in the FOR group (0.040 per patient/year; $p = 0.008$) (Table 6). In this trial the COPD exacerbations leading to hospitalisation rates were low (3% - 6%) compared to the estimates available in the current literature (up to 10%)².
- 6.24 Furthermore, change in from baseline in dyspnoea score (week 48) and change from baseline in total SGRQ score (Week 48) were not statistically significant between BEC/FOR and BUD/FOR as well as BEC/FOR and FOR. However, patients in BUD/FOR group had greater changes in dyspnoea score (-0.19 vs -0.14) and SGRQ score (-4.67 vs -3.70) than those in BEC/FOR group. Lastly, there were no significant differences in changes in symptom free days and use of rescue medications between BEC/FOR and BUD/FOR, and BEC/FOR and FOR treatment group.

Comparative harms

- 6.25 The safety results reported in the FUTURE and Calverley et al. (2010) trials are summarised in Table 7.

² Montserrat-Capdevila, J., Godoy, P., Marsal, J.R. and Barbé, F., 2015. Predictive model of hospital admission for COPD exacerbation. *Respiratory care*, 60(9), pp.1288-1294

Table 7: Summary of key adverse events in the FUTURE and Calverley et al. (2010) trials

Outcomes	FUTURE				Calverley et al. (2010)					
	BEC/FOR n=211		FP/SAL n=208		BEC/FOR n= 236		BUD/FOR n=242		FOR n= 238	
	No. patients (%)	No. events	No. patients (%)	No. events	No. patients (%)	No. events	No. patients (%)	No. events	No. patients (%)	No. events
TEAEs	36 (17.1%)	58	46 (22.1%)	76	101 (42.8%)	233	99 (40.9%)	196	105 (44.1%)	197
Serious TEAEs	4 (1.9%)	4	13 (6.3%)	16	24 (10.2%)	33	19 (7.9%)	27	14 (5.9%)	19
Treatment-emergent ADRs	6 (2.8%)	9	2 (1.0%)	3	22 (9.3%)	37	12 (5.0%)	18	20 (8.4%)	24
Severe TEAEs	2 (0.9%)	2	5 (2.4%)	5	N/A	N/A	N/A	N/A	N/A	N/A
TEAEs resulting in study drug discontinuation	3 (1.4%)	3	5 (2.4%)	5	9 (3.8%)	14	6 (2.5%)	9	5 (2.1%)	7
TEAEs leading to death	1 (0.1%)	1	0 (0.0%)	0	2 (0.8%)	2	4 (1.7%)	4	N/A	N/A

Abbreviations: TEAE= Treatment-emergent adverse events; BEC= Beclometasone dipropionate; BUD= Budesonide; FOR= Formoterol fumarate dehydrate; FP= Fluticasone propionate; SAL= Salmeterol; ADR= Adverse Drug Reaction.

N/A means the submission did not provide information.

Source: Table 56, p83 of the submission, and p86 of the CSR.

6.26 Serious treatment-emergent adverse events (TEAEs) occurred significantly less often in the BEC/FOR group than in the FP/SAL group (4 people [1.9%] compared with 13 people [6.3%], $p=0.024$). All other results in Table 7 were non-significant at the 5% level. In summary, the safety results for BEC/FOR and FP/SAL were similar.

6.27 There were no significant differences in the rates of TEAEs between the three treatments in the Calverley et al (2010) trial. The most commonly reported adverse event was exacerbation or worsening of COPD, which occurred in 27–28% of participants. The safety results in the Calverley et al. (2010) trial were similar between treatments and are in line with the expected findings for ICS/LABA combination treatments.

6.28 TEAEs leading to death occurred in only one patient in the FUTURE trial, who was in the BEC/FOR group. The submission claimed that the death was attributed to acute myocardial infarction and was not related to treatment. The Calverley et al. (2010) trial reported two deaths in the BEC/FOR group and four deaths in the BUD/FOR group.

Clinical claim

6.29 The submission described BEC/FOR as non-inferior in terms of effectiveness compared to FP/SAL and compared to BUD/FOR. The clinical claim was broadly supported by TDI and lung function results but may not be supported by the results of the rates of exacerbations.

- 6.30 The claim of non-inferior clinical effectiveness was supported by the TDI results of the FUTURE trial. However, the trial was of 12 weeks duration only and may be too short to give an accurate estimate of the effect of treatment on the key clinical outcomes. The ESC agreed with the PSCR that PBAC had previously accepted non inferiority for fluticasone furoate plus vilanterol based on a 12-week study (paragraph 6.9, fluticasone furoate plus vilanterol PSD, July 2014 PBAC Meeting).
- 6.31 The claim of non-inferior clinical effectiveness was also supported by the change in pre-dose morning FEV1 from baseline to 48 weeks reported in the Calverley et al. (2010) trial for BEC/FOR versus BUD/FOR (see paragraph 6.20).
- 6.32 A non-inferiority margin was not proposed for the co-primary outcome of mean rate per patient/year for COPD exacerbations in the Calverley et al. (2010) trial. While no significant statistical differences were evident, the upper 95% confidence interval of the exacerbation rate ratio for BEC/FOR versus BUD/FOR was high, at 1.33. However, the reduction in exacerbations was much less than anticipated in the power calculations, thus it is likely that the study was underpowered for this outcome.
- 6.33 Furthermore, the submission described BEC/FOR as non-inferior in terms of safety compared to FP/SAL and BUD/FOR. The overall safety profiles of BEC/FOR and FP/SAL in the FUTURE trial and BEC/FOR and BUD/FOR in the Calverley et al. (2010) trial were similar. No significant differences were found between the treatments apart from a significantly higher incidence of serious TEAEs in the FP/SAL treatment group (1.9% BEC/FOR vs 6.3% FP/SAL; $p = 0.024$).
- 6.34 The PBAC agreed with the ESC that the clinical claims of non-inferior effectiveness and safety were supported by the data presented.

Economic analysis

- 6.35 The cost-minimisation analysis was based on the claim of non-inferior effectiveness and safety for BEC/FOR compared to FP/SAL on the equipotent doses demonstrated in the FUTURE trial. A cost-minimisation approach is consistent with the clinical claim.
- 6.36 The equi-effective doses are presented in Table 8.

Table 8: Data used to calculate the equi-effective doses

Treatment	Dose/Day	Pack size	Days per pack
Equi-effective doses			
BEC/FOR (100/6 µg)	Two actuations twice daily	120 doses	30
FP/SAL (250/25 µg)	Two actuations twice daily	120 doses	30

Abbreviations: BEC = beclometasone dipropionate, FOR = formoterol fumarate, FP= Fluticasone propionate, SAL= Salmeterol.
Source: Section 3.2 p97 of the submission.

- 6.37 The proposed equi-effective doses were consistent with the doses and treatment regimens in the TGA Product Information for BEC/FOR and FP/SAL. However, FP/SAL 500/50 µg one actuation twice daily was used in the FUTURE trial. The submission implicitly assumed a dose intensity of 100% for both treatments, and this was a reasonable assumption given the dose intensities in the FUTURE trial.

6.38 The results of the cost-minimisation analysis as presented in the submission are shown in Table 9.

Table 9: Results of the cost-minimisation analysis

	BEC/FOR 100/6 µg	FP/SAL 250/25 µg
Inhalations per day	4	4
Actuations per inhaler	120	120
Days per pack	30	30
Packs per year		12.175
AEMP (\$)		46.78
DPMQ (\$)		62.38
Cost per year (\$)		759.48
Difference in cost per year	\$0.00	

Abbreviations: BEC= Beclometasone dipropionate; FOR= Formoterol fumarate dehydrate; FP= Fluticasone propionate; SAL= Salmeterol; AEMP= Approved ex-manufacturer price; DPMQ= Dispensed price for maximum quantity.

Source: Table 68, p98 of the submission.

6.39 The submission assumed an AEMP of FP/SAL of \$46.78 (Table 9). However, the Price Disclosure Reductions for the 2022 April Cycle suggests that this price may reduce by 12.67%³, to \$40.85.

6.40 The submission proposed an AEMP of \$█ for BEC/FOR equal to the average of the cost-minimised price of \$46.78 for COPD and the price of \$█ for the asthma indication, weighted by the project utilisation in the two indications. The submission calculated the weightings across indications, based on the split of asthma (█%) and COPD (█%) prescriptions for Seretide MDI 250/25 (FP/SAL, PBS item 8915J), using the PBS 10% Sample data. The submission stated this approach was justified as Seretide MDI 250/25 was the most likely product to be replaced in practice. Given the asthma and COPD listings are both under the same Authority Required (STREAMLINED) PBS item number and differentiated only by the streamlined authority code in each restriction, the reliability of streamlined authority code data to accurately capture prescribing for asthma and COPD is uncertain. The weighted price calculation is presented in Table 10.

Table 10: Weighted average price calculation

	COPD	Asthma
AEMP	\$█	\$29.69
Projected Utilisation	█%	█%
Weighted Average Price		\$█

Abbreviations: AEMP= Approved ex-manufacturer price; COPD= Chronic obstructive pulmonary disease.

Source: Section 3.2 p97 of the submission

6.41 Should the PBAC accept the clinical claim of overall non-inferior effectiveness and safety, the cost-minimisation approach must establish that the cost per patient for treatment with BEC/FOR would be no more than the cost per patient of any other available ICS/LABA inhaler. By analogy, the PBAC has considered that the cost for any

³ <https://www.pbs.gov.au/info/industry/pricing/price-disclosure-spd/price-disclosure-reductions-for-2022-april-cycle>

triple therapy inhalers should be no greater than the lowest price combination of ICS, LAMA and LABA products listed for COPD (paragraph 7.8, FF/UMEC/VI Trelegy, PSD December 2017 PBAC meeting; paragraph 7.2, BEC/GLY/FOR Trimbrow, PSD November 2020 PBAC meeting). The cost per patient takes into account the mean equi-effective doses of the new intervention and the alternative therapies. Where these cost per patient calculations are uncertain, the guiding principle is that the Australian Government should not bear the financial risk of this uncertainty because the Australian population already has access to therapy that is at least as effective and safe.

- 6.42 The AEMP per 30 days of four ICS/LABA inhalers are lower than the proposed indication-specific AEMP per 30 days for BEC/FOR of \$ \downarrow (Table 11). The lowest AEMP per 30 days of \$24.45 corresponds to BUD/FOR 400/12 (Symbicort Turbuhaler; DuoResp Spiromax; BiResp Spiromax).
- 6.43 BUD/FOR 400/12 with a dose of one puff twice per day and a total of 120 (2 x 60) actuations per prescription provides for 60 days of treatment. The PSCR noted that the July 2020 PSD for consideration of BEC/FOR 100/6 (Fostair) for asthma state ‘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)’⁴ (paragraph 6.26, July 2020 PBAC PSD, beclometasone + formoterol). Given this precedent, the PSCR concluded that the comparator treatment should provide 30 days of treatment per prescription and hence BUD/FOR 400/12 is not an appropriate comparator.
- 6.44 The ESC noted the issue raised by the PBAC in July 2020 related to the equi-effective doses and that based on established relativities the equi-effective doses for BEC/FOR 100/6 2 BD should be BUD/FOR 100/3 MDI 4 BD (for which one prescription provides 30 days of treatment) rather than BUD/FOR 200/6 2 BD (for which one prescription provides 60 days of treatment).
- 6.45 In November 2010 the PBAC determined for COPD the equi-effective doses are BUD/FOR 400/12 BD = FP/SAL 500/50 BD and this was on the basis of 1 prescription for BUD/FOR 400/12 providing 2 months of treatment compared with 1 month of treatment for FP/SAL 500/50⁵. On the basis of this previously established relativity, the ESC considered BUD/FOR 400/12 to be a reasonable alternative treatment, i.e. :
- BEC/FOR 100/6 2 BD = FP/SAL 250/25 2 BD = FP/SAL 500/50 BD = BUD/FOR 400/12 BD.

⁴ Corrected quote. PSCR quote “a reasonable comparator 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).”

⁵ [Pharmaceutical Benefits Scheme \(PBS\) | Budesonide with eformoterol fumarate dihydrate, powder for oral inhalation, fixed dose combination, 400 micrograms-12 micrograms per dose, Symbicort Turbuhaler 400/12®](#)

6.46 The PBAC noted the arguments provided in the PSCR and reiterated in the pre-PBAC response regarding comparable alternatives based on duration of treatment provided. On the basis of its previous COPD recommendation outlined in paragraph 6.45, the PBAC agreed with the ESC that BUD/FOR 400/12 was a reasonable alternative irrespective of treatment duration per prescription.

Table 11: ICS/LABA inhalers PBS-listed for COPD

PBS item	Brand name	Strength & Form	AEMP per 30 days	DPMQ per 30 days
8519J	Seretide 250/25; Cipla 250/25; Pavtide; SalplusF Inhaler 250/25; Seroflo 250/25	fluticasone 250 µg/actuation + salmeterol 25 µg/actuation inhalation, two puffs twice a day, 120 actuations	\$46.78	\$66.38 ^a
8432T	Seretide Accuhaler 500/50; Pavtide Accuhaler 500/50	fluticasone 500 µg/actuation + salmeterol 50 µg/actuation powder for inhalation, one puff twice a day, 60 actuations	\$46.78	\$62.38
10018G	Symbicort Rapihaler 200/6	budesonide 200 µg/actuation + formoterol fumarate dihydrate 6 µg/actuation inhalation, two puffs twice a day, 120 actuations	\$27.87	\$36.01^b
8750M	Symbicort Turbuhaler 400/12	budesonide 400 µg/actuation + formoterol fumarate dihydrate 12 µg/actuation powder for inhalation, one puff twice a day, 2 x 60 actuations	\$24.45	\$32.33
11301T	DuoResp Spiromax; BiResp Spiromax 400/12	budesonide 400 µg/actuation + formoterol fumarate dihydrate 12 µg/actuation powder for inhalation, one puff twice a day, 2 x 60 actuations	\$24.45	\$32.33
11124L	Breo Ellipta 100/25	fluticasone fumarate 100 µg/actuation + vilanterol 25 µg/actuation powder for inhalation, once puff daily, 30 actuations	\$41.88	\$57.11

Sources: Constructed during the evaluation using Table 66 submission and PBS pricing calculator (as of 29 Nov 2021) and TGA Product Information for each item. Ex-manufacturer price data: <https://www.pbs.gov.au/info/industry/pricing/ex-manufacturer-price> Pharmaceutical Benefits Schedule Item Reports: http://Medicarestatistics.Humanservices.Gov.Au/Statistics/Pbs_Item.Jsp

^a Additional charge for this brand is \$4 for Seretide 250/25 (<https://www.pbs.gov.au/medicine/item/8519J>)

^b Estimated from total number of actuations divided by number of actuations per day. Noting the maximum quantity is 2 but there is only 1 in a pack.

Bold values indicate ICS/LABAs with AEMP per 30 days less than for BEC/FOR.

Drug cost/patient/course/year

6.47 The submission proposed an annual DPMQ of BEC/FOR of \$█. This assumed █ scripts per year at the requested DPMQ of \$█. The estimated annual DPMQ for the comparator FP/SAL, was also \$759.48 (Table 9).

Estimated PBS usage & financial implications

6.48 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 for COPD. The evaluation considered this was reasonable. Key inputs used in the financial estimates are presented in Table 12.

Table 12: Data sources and parameter values applied in the utilisation and financial estimates

Data	Input	Source	Comment
Market size of BEC/FOR data			
ICS/LABA therapies indicated for COPD	8519J – FP/SAL 8432T – FP/SAL 10018G – BUD/FOR 8750M – BUD/FOR 11301T – BUD/FOR 11124L – FF/VI	PBS Schedule	This is reasonable. These represent all the PBS-listed ICS/LABA treatments for COPD.
Total PBS+RPBS units dispensed (COPD related services only)	8432T – 79,038 8519J – 258,060 8750M – 83,904 10018G – 96,515 11301T – 13,645 11124L – 73,965	Medicare Statistics PBS Item reports (2020)	This is reasonable.
Proportion of COPD scripts for ICS/LABA therapies	8432T – 23.82% 8519J – 22.01% 8750M – 25.17% 10018G – 22.38% 11301T – 28.45% 11124L – 23.57%	PBS 10% Medicare Sample Dataset (2018)	Unable to verify. The method used to estimate the indication split for ICS/LABA therapies (restricted for both asthma and COPD) is reasonable.
COPD market growth rate	-9.41%	PBS 10% Medicare Sample Dataset (2015 to 2020)	This approach is reasonable. However, the 3 year (more recent) growth rate of COPD market was -11.72% (calculated using the same data during evaluation).
BEC/FOR annual rate of displacement (2022 – 2027)	8519J – 5-20% 8432T – 5-20% 10018G – 1-2% 8750M – 1-2% 11301T – 1-2% 11124L – 1-2%	Assumed	This is uncertain. The submission did not present a rationale for these displacement rates.
BEC/FOR daily dosage	2 inhalations twice-daily; 4 actuations total	BEC/FOR PI	This is reasonable. Consistent with pivotal trials and PI.
BEC/FOR actuations per inhaler	120	BEC/FOR PI	This is reasonable. Consistent with pivotal trials and PI.
BEC/FOR days per pack	30	BEC/FOR PI	This is reasonable. Consistent with PI.
BEC/FOR unit equivalence against alternatives	BEC/FOR – 1 8519J - 1 8432T - 1 10018G – 0.5 8750M – 0.5 11301T – 0.5 11124L - 1	Calculated by the sponsor from dosages reported in the PIs. The value refers to the number of scripts per month.	This is reasonable. Consistent with PI.
BEC/FOR DPMQ	\$ [REDACTED]	Proposed.	This is the proposed average price of BEC/FOR over the COPD and asthma indications, weighted by utilisation in the indications.
MBS costs	Nil	Assumption	This is reasonable

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Data	Input	Source	Comment
Patient co-payment			
Beneficiary Type	Average patient co-payment PBS- \$17.74	PBS service volumes of the ICS/LABA COPD market from 2020	This is reasonable.
	Average patient co-payment RPBS- \$4.24		

Abbreviations: AEMP= Approved ex-manufacturer price; DPMQ= Dispensed price for maximum quantity; BEC= Beclometasone dipropionate; BUD= Budesonide; FOR= Formoterol fumarate dehydrate; FP= Fluticasone propionate; SAL= Salmeterol; COPD= Chronic obstructive pulmonary disease; FF= Fluticasone fumarate; VI= Vilanterol trifrenatate; PI = Product Information; LABA= long-acting β -agonist; ICS= inhaled corticosteroid.

Source: Table 76-78, p104-107 of the submission.

6.49 The estimated financial implications for the listing of BEC/FOR based on the following three separate DPMQs for BEC/FOR are presented in Table 13: weighted average value of \$1 as presented in the submission, indication-specific value of \$1 and least-cost alternative value of \$1 (Table 11).

Table 13: Estimated use and financial implications of listing BEC/FOR for COPD

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

Abbreviations: BEC = beclometasone dipropionate; BUD = budesonide; FF = fluticasone fumarate; FOR = formoterol fumarate; FP = fluticasone propionate; MBS = Medicare Benefits Schedule; MF = mometasone fumarate; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; SAL = salmeterol; VI = vilanterol

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

^b The dispensed price for maximum quantity (DPMQ) = \$█, which equates to indication specific price (AEMP of \$█).

^c For this calculation the dispensed price for maximum quantity (DPMQ) = \$█, which equates to that of BUD/FOR (Symbicort Turbuhaler 400/12) and BUD/FOR (DuoResp Spiromax 400/12).

Source: Table 79 and 86 of the submission.

The redacted values correspond to the following ranges:

¹ 10,000 to < 20,000

² \$0 to < \$10 million

³ 30,000 to < 40,000

⁴ 40,000 to < 50,000

6.50 The total cost to the PBS/RPBS of listing BEC/FOR was estimated to be \$0 to < \$10 million in year 1, \$0 to < \$10 million in Year 6, and a total of

\$0 to < \$10 million in the first 6 years of listing using a weighted average DPMQ of \$1. The net saving of listing BEC/FOR over the first 6 years was estimated as \$0 to < \$10 million. Assuming the proposed weighted average price applies to the asthma indication, the submission predicted an additional cost of \$0 to < \$10 million over 6 years in the asthma indication.

- 6.51 When the indication specific price (DPMQ \$62.38) is used the total cost to the PBS/RPBS of listing BEC/FOR was estimated to be \$0 to < \$10 million in year 1 and \$0 to < \$10 million in year 6, with a total of \$10 million to < \$20 million in the first 6 years of listing. The expected total net additional cost to the government over the first six years of the listing is \$0 to < \$10 million.
- 6.52 When pricing for the least costly alternative (DPMQ \$32.33) is used, the total cost to the PBS/RPBS of listing BEC/FOR was estimated to be \$0 to < \$10 million in year 1 and \$0 to < \$10 million in year 6, with a total of \$0 to < \$10 million over the first 6 years of listing. The expected total net savings over the first six years was estimated as \$0 to < \$10 million.

Quality Use of Medicines

- 6.53 The submission claimed that listing of BEC/FOR for COPD will not require any alterations to the treatment algorithm and will put BEC/FOR at Step 3 of the COPD management plan as an alternative to other ICS/LABA therapies. Given the number and complexity of respiratory devices currently available in Australia, there is a risk for consumers in terms of confusion regarding correct inhalers use.

Financial Management – Risk Sharing Arrangements

- 6.54 The submission did not propose a risk-sharing arrangement.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority Required (STREAMLINED) listing of the fixed-dose combination (FDC) of beclomethasone (BEC) with formoterol (FOR) for the treatment of chronic obstructive pulmonary disease (COPD).
- 7.2 The PBAC considered the claim of non-inferior effectiveness and safety to the FDC of fluticasone propionate (FP) 250 µg with salmeterol (SAL) 25 µg was reasonable. However, the PBAC considered for purposes of satisfying Section 101(3B) of the *National Health Act 1953*, any high dose inhaled corticosteroid (ICS) with long-acting beta2-agonist (LABA) FDC are relevant alternative therapies. The PBAC's recommendation was therefore, among other matters, based on its assessment that the cost of BEC/FOR should be no greater than the lowest price combination of the PBS listed components of ICS/LABA therapy that are available for COPD at comparable doses, irrespective of the days of treatment provided.
- 7.3 The PBAC noted the input from the Lung Foundation of Australia, which supported the

listing of BEC/FOR in COPD.

- 7.4 The PBAC considered FP/SAL 250/25 µg FDC to be an appropriate comparator. In addition, the PBAC also considered all ICS/LABA FDCs listed for COPD at comparable doses were appropriate alternative therapies (see paragraph 5.3).
- 7.5 The PBAC considered the claim of non-inferior effectiveness was supported by the Transition Dyspnoea Index (TDI) results of the FUTURE trial. The claim was also supported by the change in pre-dose morning FEV1 from baseline to 48 weeks reported in the Calverly et al. (2010) trial for BEC/FOR versus budesonide (BUD) with FOR. The PBAC considered that the upper 95% confidence interval for the mean rate of COPD exacerbations in the Calverly et al. (2010) trial was high, at 1.33 but acknowledged that the study was likely underpowered for this outcome. Overall, the PBAC considered the claim of non-inferior effectiveness was reasonable.
- 7.6 The PBAC considered that the evidence presented in the submission supported the claim of non-inferior comparative safety.
- 7.7 The PBAC noted that the submission presented a cost-minimisation analysis between BEC/FOR and FP/SAL. The PBAC accepted the equi-effective doses outlined in Table 8 as the basis for the analysis. However, the PBAC considered the cost of BEC/FOR should be no greater than the lowest price combination of the PBS listed components of ICS/LABA therapy that are available for COPD at the comparable doses outlined in Table 11, irrespective of the days of treatment provided (see paragraph 6.46).
- 7.8 The PBAC noted the estimated financial implications for listing based on three separate DPMQs for BEC/FOR: weighted average value; indication-specific value; and least-cost alternative value (see Table 13). The PBAC considered that concerns regarding the appropriate DPMQ for use in the financial estimates were addressed by the Committee's recommendation that BEC/FOR be listed on a cost-minimisation basis against the least costly ICS/LABA FDC as outlined in paragraph 7.7.
- 7.9 The PBAC noted the following flow-on restriction changes to the current BEC/FOR listing for asthma (12183F):
- Remove administrative advice 'This drug is not PBS-subsidised for the treatment of chronic obstructive pulmonary disease (COPD)'.
 - Move all administration advice from the PR level to the indication level.
- 7.10 The PBAC advised that under Section 101(3BA) of the *National Health Act 1953* BEC/FOR should be treated as interchangeable on an individual basis with other appropriate ICS/LABA FDC products on the PBS.
- 7.11 The PBAC advised that BEC/FOR is suitable for prescribing by nurse practitioners.
- 7.12 The PBAC recommended that the Early Supply Rule should not apply.
- 7.13 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.

7.14 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 indication to BEC/FOR for 'COPD' as follows:

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Name and Manufacturer
BECLOMETASONE with FORMOTEROL beclometasone dipropionate 100 microgram/actuation + formoterol (eformoterol) fumarate dihydrate 6 microgram/actuation inhalation, 120 actuations	12183F	1	1	5	Fostair® Chiesi Australia Pty Ltd

Restriction Summary / Treatment of Concept:

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required - Streamlined
Condition: Chronic obstructive pulmonary disease (COPD)
Indication: Chronic obstructive pulmonary disease (COPD)
Clinical criteria: Patient must have significant symptoms despite regular long-acting bronchodilator therapy
AND
Clinical criteria: Patient must have experienced at least one severe exacerbation, which required hospitalisation, or two or more moderate exacerbations in the 12 months prior to commencing treatment for COPD
Administrative Advice: This product is not indicated for the initiation of bronchodilator therapy in COPD.
Administrative Advice: The treatment must not be used in combination with LABA monotherapy or LAMA/LABA combination therapy.
Administrative Advice: A LAMA/LABA includes acclidinium/formoterol, glycopyrronium/indacaterol, tiotropium/olodaterol, or umeclidinium/vilanterol.
Administrative Advice:

Diagnosis of COPD should include measurement of airflow obstruction using spirometry, with confirmation of post-bronchodilator airflow obstruction.

8.2 Flow-on changes to the current PBS listing for asthma (12183F):

- Remove administrative advice ‘This drug is not PBS-subsidised for the treatment of chronic obstructive pulmonary disease (COPD)’.
- Move all administration advice from the PR level to the indication level.

Restriction Summary / Treatment of Concept:

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required - Streamlined
Condition: Asthma
Indication: Asthma
Clinical criteria: Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids
AND
Population Criteria Patient must be aged 18 years or older
Administrative Advice: This product is not indicated for the initiation of treatment in asthma
Administrative Advice: This drug is not PBS-subsidised for the treatment for chronic obstructive disease (COPD).
Administrative Advice: The patient must not be on a concomitant single agent long-acting-beta-2-agonist (LABA)
Administrative Advice: A LABA includes olodaterol, indacaterol, salmeterol, formoterol or vilanterol.
Administrative Advice: Adherence to current treatment and device (inhaler) technique should be reviewed at each clinical visit and before “stepping up” a patient’s medication regimen,
Administrative Advice: This product is not PBS-subsidised for use as ‘maintenance and reliever’ therapy.
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.