

5.01 ACLIDINIUM BROMIDE PLUS EFORMOTEROL FUMARATE DIHYDRATE

dry powder inhaler, 340 µg plus 12 µg per actuation, 60 actuations

Brimica® Genuair®

A. Menarini Australia Pty Ltd.

1 Purpose of Application

- 1.1 The submission requested Authority Required listing for acclidinium/eformoterol fixed dose combination (FDC) for treatment of chronic obstructive pulmonary disease (COPD).

2 Requested listing

- 2.1 The requested listing is presented below. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed for Max. Qty	Price	Proprietary Manufacturer	Name and
ACLIDINIUM + EFORMOTEROL aclidinium 340 microgram/actuation + eformoterol 12 microgram/actuation inhalation: powder for, 60 actuations	1	5	\$ [REDACTED]		Brimica® Genuair®	A. Menarini

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	-
Condition:	Chronic obstructive pulmonary disease (COPD)
PBS Indication:	Chronic obstructive pulmonary disease (COPD)
Treatment phase:	-
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have been stabilised on a combination of a long acting muscarinic antagonist and long acting beta-2 agonist.

Administrative Advice	<p>The treatment must not be used in combination with an ICS/LABA, or LAMA or LABA monotherapy.</p> <p>A LAMA includes tiotropium, glycopyrronium, aclidinium or umeclidinium.</p> <p>A LABA includes indacaterol, salmeterol, eformoterol or <i>vilanterol</i>.</p> <p>This product is not PBS-subsidised for the treatment of asthma.</p> <p>This product is not indicated for the initiation of bronchodilator therapy in COPD.</p>
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- 2.2 The requested listing was based on a cost-minimisation analysis versus glycopyrronium/indacaterol FDC and umeclidinium/vilanterol FDC.

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

3 Background

- 3.1 TGA status: The submission was made under TGA/PBAC Parallel Process. The TGA approved the registration of aclidinium/eformoterol on 17 April 2015. At the time of PBAC consideration all relevant data were available.
- 3.2 This product had not been previously considered by the PBAC. Aclidinium was recommended for listing by the PBAC in March 2014. Eformoterol is not listed as monotherapy for the treatment of COPD, however it is PBS listed in combination with budesonide (inhaled corticosteroid).

4 Clinical place for the proposed therapy

- 4.1 Aclidinium/eformoterol FDC would provide an alternative for other available long-acting muscarinic receptor antagonist (LAMA) / long-acting selective β_2 agonist (LABA) FDCs for mild, moderate and severe COPD, as defined by the Lung Foundation Australia 2014 clinical guidelines.

5 Comparator

- 5.1 The nominated comparators were glycopyrronium/indacaterol FDC and umeclidinium/vilanterol FDC. The submission nominated aclidinium monotherapy and eformoterol monotherapy as supportive comparators. The PBAC considered that the comparators were appropriate.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

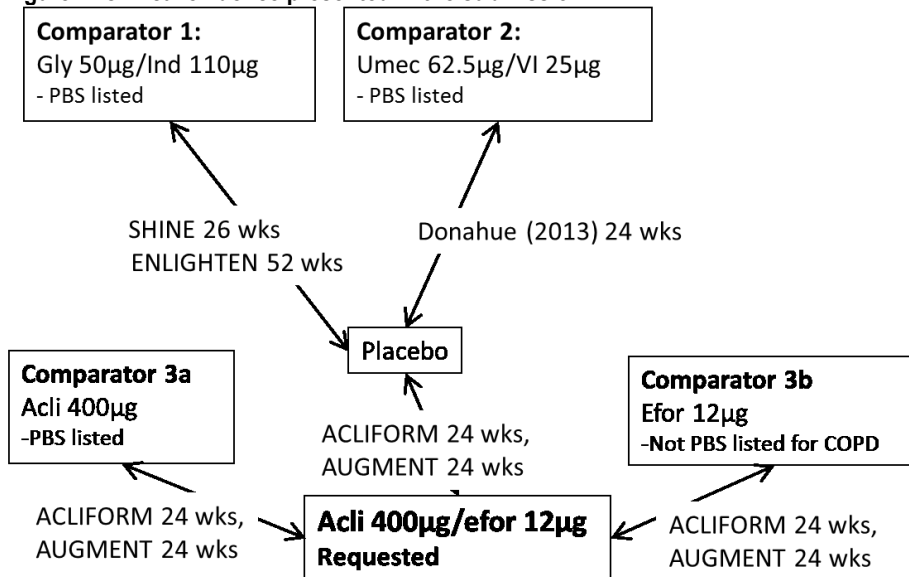
Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission relied on five placebo-controlled trials of three treatments (aclidinium/eformoterol FDC, glycopyrronium/indacaterol FDC and umeclidinium/vilanterol FDC). The trials are presented in Figure 1 below. However, the key evidence was based on a network meta-analysis that comprised six placebo-controlled trials. One trial included tiotropium 18 µg plus eformoterol 10 µg which was not presented in the submission as a comparator. Additionally, the submission presented efficacy and safety of aclidinium/eformoterol FDC compared to its individual constituent products. This analysis was based on two trials, which were included in the above network meta-analysis.

Figure 1: Clinical evidence presented in the submission



Source: Compiled during evaluation

Acli = aclidinium; Efor = eformoterol; Gly = glycopyrronium; Ind = indacaterol; Umec = umeclidinium; Vi = vilanterol; wks = weeks; PBS = Pharmaceutical Benefits Scheme; COPD = chronic obstructive pulmonary disease

6.4 Details of the five trials included in the network meta-analysis used for the generation of the key evidence are provided in the following table.

Table 1: Trials presented in the submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Acclidinium/eformoterol FDC vs. placebo		
ACLIFORM	Efficacy And Safety Of Acclidinium Bromide/Eformoterol Fumarate Fixed-Dose Combinations Compared With Individual Components And Placebo When Administered To Patients With Stable Chronic Obstructive Pulmonary Disease. Clinical Study Report M/40464/30R. Singh D, Jones PW, Bateman ED, <i>et al.</i> Efficacy and safety of acclidinium bromide/formoterol fumarate fixed-dose combinations compared with individual components and placebo in patients with COPD (ACLIFORM-COPD): a multicentre, randomised study.	19 August 2013 NCT01462942 <i>BMC Pulm Med</i> 2014; 14(1): 178
AUGMENT	A Phase III, Randomized, Double-Blind, Placebo-Controlled Study Evaluating The Efficacy, Safety, And Tolerability Of Two Fixed-Dose Combinations Of Acclidinium Bromide/Eformoterol Fumarate Compared With Acclidinium Bromide, Eformoterol Fumarate And Placebo For 24-Weeks Treatment In Patients With Moderate To Severe, Stable Chronic Obstructive Pulmonary Disease (COPD) (AUGMENT COPD). Clinical Study Report LAC-MD-31. D'Urzo AD, Rennard SI, Kerwin EM, <i>et al.</i> Efficacy and safety of fixed-dose combinations of acclidinium bromide/formoterol fumarate: the 24-week, randomized, placebo-controlled AUGMENT COPD study.	28 August 2013 NCT01437397 <i>Respir Res</i> 2014; 14(15):123 [abstract]
Glycopyrronium/indacaterol FDC vs. placebo		
SHINE	Bateman ED, Ferguson GT, Barnes N, <i>et al.</i> Dual bronchodilation with QVA149 versus single bronchodilator therapy: The SHINE study.	<i>Eur Respir J</i> 2013; 42(6): 1484-1494 NCT01202188
ENLIGHTEN	Dahl R, Chapman KR, Rudolf M, <i>et al.</i> Safety and efficacy of dual bronchodilation with QVA149 in COPD patients: The ENLIGHTEN study.	<i>Respir Med</i> 2013; 107(10): 1558-1567 NCT01120717
Umeclidinium/vilanterol FDC vs. placebo		
Donohue (2013)	Donohue JF, Maleki-Yazdi MR, Kilbride S, <i>et al.</i> Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. GSK-DB2113373	<i>Respir Med</i> 2013; 107(10): 1538-1546 NCT01313650

Source: Table B-3, p26; Table B-49, p74 of the submission
COPD = chronic obstructive pulmonary disease; FDC = fixed-dose combination

- 6.5 The key features of the randomised trials are summarised in Table 2 below. Patients treated with umeclidinium/vilanterol FDC had slightly more severe COPD, as defined by the predicted FEV₁.

Table 2: Key features of the included evidence – indirect comparison

Trial	N ^a	Design/ duration	Risk of bias	Patient population	Outcomes
Acclidinium/eformoterol FDC vs. placebo					
ACLIFORM	579	R, DB, 24 wks	Low	COPD	Trough FEV ₁
AUGMENT	675	R, DB, 24 wks	Low	FEV ₁ predict. <80%, ≥30%	1-hour post-dose FEV ₁
Glycopyrronium/indacaterol FDC vs. placebo					
SHINE	709	R, DB, 26 wks	Low	COPD FEV ₁ predict. <80%, ≥30%	Trough FEV ₁
ENLIGHTEN	339	R, DB, 52 wks	Low		Adverse events Pre-dose FEV ₁
Umeclidinium/vilanterol FDC vs. placebo					
Donohue (2013)	694	R, DB, 24 wks	Low	COPD FEV ₁ predict. <70%	Trough FEV ₁

Source: Table 5, pp30-32 of the Technical Document 2 attachment to the submission

FDC = fixed dose combination; R = randomised; DB = double blind; wks = weeks; COPD = chronic obstructive pulmonary disease; FEV₁ = forced expiratory volume in one second; FVC = forced vital capacity; predict = predicted

^a numbers of patients randomised in treatment arms relevant for the indirect comparison

Comparative effectiveness

- 6.6 Results of a network analysis of trough FEV₁ for the main comparisons and the supportive comparisons are presented in Tables 3 and 4, respectively. A higher trough FEV₁ indicates better lung function.

Table 3: Results of trough FEV₁ across the randomised trials

Trial ID	MD (SE)	Acli/Efor	Placebo	Placebo	Comparator	MD (SE)	Indirect
		MD (SE)	MD (SE)	MD (SE)	MD (SE)		MD (95% CI)
Acclidinium/eformoterol FDC trials							
ACLIFORM	143 (21)	83 (12)	-61 (18)				
AUGMENT	130 (18)	95 (12)	-35 (13)				
Glycopyrronium/indacaterol FDC trials					Gly/Ind		
SHINE				-50 (NR) ^a	150 (NR) ^a	200 (18)	
ENLIGHTEN				-57 (NR) ^a	95 (NR) ^a	152 (35)	
Network analysis	136 (109, 163)					190 (159, 222)	-54 (-96, -13)
Indirect comparison	136 (109, 162) <i>I</i> ² = 0%					186 (143, 229) <i>I</i> ² = 30.3%	-50 (-101, 0)
Umeclidinium/vilanterol FDC trials					Umec/Vi		
Donohue (2013)				4 (16)	171 (13)	167 (20)	
Network analysis	136 (109, 163)					167 (128, 206)	-31 (-79, 16)
Indirect comparison	136 (109, 162) <i>I</i> ² = 0%					167 (128, 206)	-31 (-79, 16)

Source: Tables B-57 to B-58, pp86-87 of the submission; calculated during evaluation using random effect methods for the meta-analyses and Bucher method for indirect comparisons

Italics information retrieved during evaluation from trial reports/publications attachments to the submission

^a calculated during evaluation from baseline pre-bronchodilator FEV₁ and trough FEV₁ at week 26

Bold = statistically significant; MD = mean difference; CI = confidence interval; NR = not reported; SE = standard error; FEV₁ = forced expiratory volume in one second; Acli/Efor = acclidinium/eformoterol FDC; Gly/Ind = glycopyrronium/indacaterol FDC; Umec/Vi = umeclidinium/vilanterol FDC; FDC = fixed dose combination; *I*² = proportion of variation across studies attributable to heterogeneity

- 6.7 The ESC noted that the individual trials included in the indirect comparison were assessed as having a low within-trial risk of bias. However, due to exchangeability issues when using these trials in an indirect comparison, there is a high risk of bias in the results of the indirect comparison.

Table 4: The results of change in trough FEV₁ (mL) from baseline to 24 weeks (direct comparison versus acclidinium monotherapy and eformoterol monotherapy)

	Acli/Efor FDC	Acli 400 µg	Efor 12 µg	Acli/Efor FDC vs. Acli	Acli/Efor FDC vs. Efor
	Mean (SE)	Mean (SE)	Mean (SE)	MD (95% CI)	MD (95% CI)
ACLIFORM	83 (12)	56 (12)	-2 (12)	26 (-7, 60)	85 (51, 119)
AUGMENT	95 (12)	66 (12)	50 (12)	28 (-6, 63)	45 (11, 79)
Pooled analysis	90 (9)	61 (9)	21 (9)	28 (4, 52)	68 (44, 92)

Source: Table B-18, p50; Table B-21, p53; Table B-34, pp60-61; Table B-40, p65; Table B-46, p70 of the submission

Bold = statistically significant; Acli = acclidinium; Efor = eformoterol; FDC = fixed dose combination; FEV₁ = forced expiratory volume in one second; CI = confidence interval; MD = mean difference; SE = standard error

- 6.8 Acclidinium/eformoterol FDC resulted in statistically significant lower trough FEV₁ at 24 weeks compared to glycopyrronium/indacaterol FDC (comparator 1), although this difference was not clinically relevant given the minimal clinically important difference of 100 to 140 mL. No statistically significant difference was observed for the comparison with umeclidinium/vilanterol FDC (comparator 2).
- 6.9 Acclidinium/eformoterol FDC was statistically significantly superior to its mono-components (comparator 3a and 3b); however, this difference was not clinically relevant. While this is similar to other FDCs, the difference between acclidinium and acclidinium/eformoterol (28 (4, 52) mL) is less than that for other FDCs, where addition of the LABA resulted in a 70mL (glycopyrronium/indacaterol) or 95mL (umeclidinium/vilanterol) increase.
- 6.10 The ESC noted that application of minimal clinically important difference to combination therapies has recently been discussed (Jones PW et al., 2014 (American Journal of Respiratory and Critical Care Medicine Vol 189, Iss 3, pp 250-255)), with consideration of the role of responder rates and responder analysis as an appropriate method in assessing clinical incremental advantage in this setting.
- 6.11 Results for COPD exacerbations did not result in statistically significant differences between acclidinium/eformoterol FDC and any of the comparators.

Comparative harms

- 6.12 The submission presented evidence of adverse events at 24 weeks and serious adverse events at 24 weeks of acclidinium/eformoterol FDC versus the main comparators (Table 5). The submission also considered an extended assessment of comparative harms. The extended information supported the results of the harms analysis.

Table 5: Safety results of network meta-analysis

Trial ID	OR (95% CrI)	Acli/Efor	PBO	PBO	Comparator	OR (95% CrI)	Indirect OR (95% CrI)
		n/N (%)	n/N (%)	n/N (%)	n/N (%)		
ADVERSE EVENTS AT 24 WEEKS							
Acridinium/eformoterol FDC trials							
ACLIFORM		194/385 (50%)	103/194 (53%)				
AUGMENT		215/335 (64%)	181/332 (55%)				
Glycopyrronium/indacaterol FDC trials				Gly/Ind			
SHINE				134/232 (58%)	261/474 (55%)		
ENLIGHTEN				64/113 (57%)	130/225 (58%)		
Network analysis	1.20 (0.95, 1.51)					0.94 (0.72, 1.22)	1.27 (0.90, 1.80)
Umeclidinium/vilanterol FDC trials				Umecl/Vi			
Donohue (2013)				130/280 (46%)	212/413 (51%)		
Network analysis	1.20 (0.95, 1.51)					1.22 (0.90, 1.65)	0.98 (0.67, 1.44)
SERIOUS ADVERSE EVENT AT 24 WEEKS							
Acridinium/eformoterol FDC trials							
ACLIFORM		23/385 (6%)	12/194 (6%)				
AUGMENT		19/335 (6%)	12/332 (4%)				
Glycopyrronium/indacaterol FDC trials				Gly/Ind			
SHINE				13/232 (6%)	22/474 (5%)		
ENLIGHTEN				12/113 (11%)	37/225 (16%)		
Network analysis	1.28 (0.77, 2.20)					1.21 (0.74, 2.00)	1.06 (0.52, 2.18)
Umeclidinium/vilanterol FDC trials				Umecl/Vi			
Donohue (2013)				9/280 (3%)	21/413 (5%)		
Network analysis	1.28 (0.77, 2.20)					1.65 (0.77, 3.89)	0.77 (0.29, 1.97)

Source: Table B-65, p93; Table B-66, pp93-94; Table B-67, pp94-95; Table B-68, p95 of the submission

Italics indicates values corrected based on Technical Document 2 attachment to the submission

OR = odds ratio; CrI = credible interval; Acli/Efor = acridinium/eformoterol FDC; Gly/Ind = glycopyrronium/indacaterol FDC; Umecl/Vi = umeclidinium/vilanterol FDC; FDC = fixed dose combination; PBO = placebo

- 6.13 The network analysis using placebo as the reference arm detected no statistically significant differences between acridinium/eformoterol FDC and its comparators in terms of odds ratios for adverse events and serious adverse events. The most common treatment emergent adverse event for acridinium/eformoterol FDC was headache and nasopharyngitis, with similar event rates for the placebo group.

Clinical claim

6.14 **Comparison 1: versus glycopyrronium/indacaterol FDC**

Comparison 2: versus umeclidinium/vilanterol FDC

The submission described acridinium/eformoterol FDC as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over glycopyrronium/indacaterol FDC and umeclidinium/vilanterol FDC.

- The appropriateness of using placebo as the common comparator arm. In all trials the discontinuation rates in the placebo arm were higher than in the active treatment arm. Placebo might not have been an adequate treatment in this setting, given that patients who had prior LAMA and/or LABA treatment experience might be able to identify placebo treatment due to lack of efficacy thus breaking the blinding. The Pre-Sub-Committee Response (PSCR) argued that FEV₁ is an objective outcome that is minimally impacted by unblinding of patients;
- Patients in the umeclidinium/vilanterol FDC trial had more severe COPD, which may impact on response to treatment, as well as interpretation of the minimal clinically important difference due to floor and ceiling effects;
- For the comparison with umeclidinium/vilanterol FDC, the efficacy and safety in the placebo arms were not comparable, limiting the appropriateness of performing an indirect comparison;
- Trial lengths of 24/26 weeks may not have been sufficient for the exacerbation rates to be a meaningful outcome measure.

6.15 **Comparison 3a: versus acclidinium monotherapy**

Comparison 3b: versus eformoterol monotherapy

The submission described acclidinium/eformoterol FDC as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over acclidinium monotherapy or eformoterol monotherapy. With respect to this claim, the ESC noted that:

- For one of the two primary endpoints, the difference in trough FEV₁ versus either comparator did not reach the minimal clinically important difference of 100 to 140 mL, despite being statistically significant. The PSCR argued that as with acclidinium/eformoterol, clinically meaningful differences in trough pre-dose FEV₁ over mono components were not reported for the comparator FDCs (glycopyrronium/indacaterol and umeclidinium/vilanterol). The ESC considered that this may be reasonable, although the difference between acclidinium and acclidinium/eformoterol was smaller than for the comparators.
- In terms of patient exacerbations no statistically significant differences were detected versus either constituent. The PSCR advised that the clinical trials were not designed to detect a treatment difference for this outcome and re-presented data from the submission on the rate of COPD exacerbations reported in the ACLIFORM and AUGMENT trials. This showed non-significant differences in the proportion of patients with an exacerbation.

Economic analysis

6.16 The submission presented a cost-minimisation analysis. The equi-effective doses were estimated as:

- acclidinium/eformoterol 340/12 µg twice daily;
- glycopyrronium/indacaterol 50/110 µg once daily; and
- umeclidinium/vilanterol 62.5/25 µg once daily.

The equi-effective doses were trial-based. This was appropriate.

6.17 The proposed drug and the comparators were all ongoing treatments offering 30 days of treatment per pack at the same dispensed price for maximum quantity (DPMQ) of \$96.38. The analysis assumed no differences in healthcare resource

utilisation, drug administration, management of adverse events or other treatments of COPD. This seemed reasonable.

- 6.18 The submission also presented a cost-minimisation analysis versus acclidinium plus eformoterol provided as two prescriptions. The submission estimated that the cost for the FDC would be lower than the two products (\$96.38 vs. \$99.04, respectively). This comparison was not relevant, as the submission did not provide evidence of non-inferior efficacy and the DPMQ price for eformoterol 12 µg was for the asthma indication. Eformoterol monotherapy was not listed for the treatment of COPD.

Drug cost/patient/year: \$1,173

- 6.19 Acclidinium/eformoterol FDC is an ongoing treatment. The drug cost per patient per year was calculated as 12.17 30-day packs per year at a DPMQ of \$96.38. This calculation was the same for the two main comparator drugs glycopyrronium/indacaterol FDC and umeclidinium/vilanterol FDC.

Estimated PBS usage & financial implications

- 6.20 This submission was not considered by the DUSC. The submission took a mixed epidemiological and market share approach to calculating the financial impacts. This was due to the immaturity of the LAMA/LABA FDC market. Key sources of information used in the submission were:
- Australia Bureau of Statistics (ABS) population size projections;
 - COPD prevalence based on self-reported evidence from an Australian sample (Toelle 2013);
 - Proportions of COPD severity and drug utilisation within severity groups based on a European and US population study (Vestbo 2014);
 - Assumptions regarding switching to LAMA/LABA FDC from other COPD treatments; and
 - Assumptions regarding the relative market shares of LAMA/LABA FDCs.

Table 6: Estimated use and financial implications

	2016	2017	2018	2019	2020
Estimated extent of use					
LAMA/LABA FDC patients					
Acli/Efor market share	%	%	%	%	%
Acli/Efor patients					
Acli/Efor packs ^a					
Estimated net cost to PBS/RPBS/MBS					
Acli/Efor cost to PBS/RPBS	\$	\$	\$	\$	\$
Change in cost of other FDC drugs	-\$	-\$	-\$	-\$	-\$
Cost to MBS	\$0	\$0	\$0	\$0	\$0
Estimated total net cost					
Net cost to PBS/RPBS/MBS	\$0	\$0	\$0	\$0	\$0

Source: Table E-13, pp127-128 of the submission

^a Assuming 12.2 packs per year as calculated by the submission

FDC = fixed dose combination; LAMA = long-acting muscarinic antagonist; LABA = long-acting selective β₂ agonist; Acli/Efor = acclidinium/eformoterol FDC; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; MBS = Medicare Benefits Schedule

The redacted table above shows that in Year 5, the estimated number of acclidinium/eformoterol FDC packs was over 200,000 and there would be zero net cost to the PBS/RPBS.

- 6.21 The submission estimated the net cost to PBS of acclidinium/eformoterol FDC listing as nil in all years, resulting from a substitution of existing FDC products and assumed no additional market growth which may not have been reasonable.
- If acclidinium/eformoterol FDC would result in a larger growth of the LAMA/LABA FDC market by replacing monotherapy, there could be a cost to the PBS.
 - The overall size of the FDC market might be an under or overestimate because the calculations were mainly based on assumptions and international data that were not verified in the Australian context. Some of the assumptions were explored in sensitivity analyses. The PSCR argued that using utilisation as presented by Henderson (2012) or current market share data from the Department of Human Services, as suggested by the evaluation, would not be appropriate as Henderson (2012) does not include the use of the primary comparators nominated in the submission and is not informative with regard to current Australian prescribing and clinical management, and market share data from the Department of Human Services does not include mature data on the primary comparators as they had been listed on the PBS for less than 6 months at the time of submission.
 - The number of packs per patient per year did not account for compliance issues. The PSCR claimed that the submission took a conservative position in assuming no compliance issues or wastage. The ESC agreed that this approach was conservative, noting that the estimated number of packs may be overestimated.

Quality Use of Medicines

- 6.22 The submission provided information regarding patient compliance in the context of satisfaction with the inhaler use. The ESC noted that the associations between treatment adherence, patient satisfaction and health outcomes (i.e. exacerbations and hospitalisations) were not reliable given the study was cross-sectional and treatment adherence was determined by participating physicians who had selected patients for study inclusion. The validity of the adherence measure could not be confirmed. Further, the impact of other treatment related factors known to influence adherence (e.g. dosing regimen, cost and side effects) were not accounted for. The association between treatment adherence and health outcomes was weak and should be interpreted with caution.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of acclidinium/eformoterol FDC as an Authority required (STREAMLINED) benefit for the treatment of chronic obstructive pulmonary disease for patients already stabilised on concomitant LAMA and LABA therapy.
- 7.2 The PBAC recommended the listing on a cost-minimisation basis to the existing LAMA/LABA fixed dose combinations, umeclidinium/vilanterol and glycopyrronium/indacaterol. The equi-effective doses are considered to be acclidinium 340 microgram with eformoterol 12 microgram (twice daily), umeclidinium

62.5 microgram with vilanterol 25 microgram (daily), and glycopyrronium 50 microgram with indacaterol 110 microgram (daily).

- 7.3 The PBAC considered that the claim of non-inferior comparative effectiveness and safety was reasonable. Noting that there was uncertainty due to the limited reliability of the indirect comparisons, the PBAC accepted that the evidence presented in the submission suggested that acclidinium/eformoterol FDC is similar in efficacy and safety to the nominated LAMA/LABA FDC comparators.
- 7.4 The PBAC considered that although the market for fixed dose combination products in COPD is growing, it was unlikely that the listing of acclidinium/eformoterol would result in any substantial additional market growth.
- 7.5 In accordance with subsection 101(3BA) of the *National Health Act* 1953, the PBAC advised that it is of the opinion that acclidinium/eformoterol should be treated as interchangeable on an individual patient basis with indacaterol/glycopyrronium and umeclidium/vilanterol.
- 7.6 In accordance with subsection 101(4AA) of the *National Health Act*, the PBAC advised that it was of the opinion that the Minister should determine a therapeutic group comprising of all LAMA/LABA fixed dose combinations including indacaterol/glycopyrronium, umeclidium/vilanterol, and acclidinium/eformoterol.
- 7.7 The PBAC advised that acclidinium/eformoterol is suitable for prescribing by nurse practitioners.
- 7.8 The PBAC recommended that the Safety Net 20 Day Rule should apply.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
ACLIDINIUM + EFORMOTEROL aclidinium 340 microgram/actuation + eformoterol 12 microgram/actuation inhalation: powder for, 60 actuations	1	5	Brimica® Genuair® A. Menarini

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	-
Condition:	Chronic obstructive pulmonary disease (COPD)
PBS Indication:	Chronic obstructive pulmonary disease (COPD)
Treatment phase:	-
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have been stabilised on a combination of a long acting muscarinic antagonist and long acting beta-2 agonist.
Administrative Advice	The treatment must not be used in combination with an ICS/LABA, or LAMA or LABA monotherapy. A LAMA includes tiotropium, glycopyrronium, aclidinium or umeclidinium. A LABA includes indacaterol, salmeterol, eformoterol or vilanterol. This product is not PBS-subsidised for the treatment of asthma. This product is not indicated for the initiation of bronchodilator therapy in COPD.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

A.Menarini Australia Pty Ltd welcomes the recommendation to list Brimica Genuair (acridinium/eformoterol FDC) as a treatment of COPD on the PBS.