

5.01 BECLOMETASONE with FORMOTEROL and GLYCOPYRRONIUM

Pressurised inhalation containing beclometasone dipropionate 100 micrograms with formoterol fumarate dihydrate 6 micrograms and glycopyrronium 10 micrograms (as bromide) per dose, 120 doses, TRIMBOW[®], Chiesi Australia Pty Ltd.

1 Purpose of submission

- 1.1 The submission requested an Authority Required (Streamlined) listing of TRIMBOW[®] pressurised metered dose inhaler (pMDI), the fixed dose combination (FDC) of beclometasone (BEC), an inhaled corticosteroid (ICS), with formoterol (FOR), a long-acting beta2-agonist (LABA), and glycopyrronium (GLY), a long-acting muscarinic antagonist (LAMA) for maintenance treatment of moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an ICS/LABA or LABA/LAMA.
- 1.2 The submission presented a cost-minimisation analysis of TRIMBOW versus Trelegy[®] Ellipta[®]. Trelegy Ellipta is the only other currently listed ICS/LABA/LAMA triple therapy for COPD. The components in Trelegy Ellipta are fluticasone furoate (FF) 100 mcg, umeclidinium (UMEC) 62.5 mcg and vilanterol (VIL) 25 mcg.
- 1.3 Table 1 summarises the key features of the submission.

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

Component	Description
Population	Adult patients with moderate to severe COPD who are not adequately treated by a combination of ICS/LABA or LABA/LAMA.
Intervention	TRIMBOW [BEC, FOR and GLY (dosing: 100 mcg /6 mcg /10 mcg)] Each delivered dose (the dose leaving the mouthpiece) contains 87 mcg of BEC, 5 mcg of FOR and 9 mcg of GLY [as 11 mcg glycopyrronium bromide].
Comparator	Trelegy Ellipta [(fluticasone furoate/umeclidinium [as bromide]/vilanterol [as trifenate]).
Outcomes	<ul style="list-style-type: none"> • COPD exacerbations (moderate to severe) <ul style="list-style-type: none"> ○ Rate over treatment period; time to first exacerbation • Lung function <ul style="list-style-type: none"> ○ Change from baseline in pre- and post-dose FEV1; pre-dose FEV1 response (change of $\geq 0.1L$) • Dyspnoea • St George Respiratory Questionnaire <ul style="list-style-type: none"> ○ Change from baseline; response (reduction ≤ 4 units) • Use of rescue medication • Safety
Clinical claim	TRIMBOW is non-inferior in terms of efficacy (COPD exacerbations) compared to Trelegy Ellipta; TRIMBOW is non-inferior in terms of safety when compared to Trelegy Ellipta. TRIMBOW is superior in terms of efficacy and non-inferior in terms of safety to ICS/LABA (BEC/FOR); superior in terms of efficacy and non-inferior in terms of safety to LAMA (tiotropium); and non-inferior in terms of efficacy and safety to ICS/LABA+LAMA (BEC/FOR + tiotropium).

BEC: Beclometasone dipropionate; COPD: Chronic Obstructive Pulmonary Disease, FEV1: Forced Expiratory Volume in the first second of expiration, FOR: Formoterol fumarate dehydrate, GLY: Glycopyrronium, ICS: Inhaled Corticosteroid, LABA: Long-Acting Beta2-Agonist, LAMA: Long-Acting Muscarinic Antagonist
Source: Table 9, pp9-10 of the submission

2 Background

Registration status

- 2.1 TRIMBOW was registered on the ARTG on 24 June 2020 (ARTG ID: 314166) for: Maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid (ICS) and a long-acting beta2-agonist (LABA) or a combination of a LABA and a long-acting muscarinic antagonist (LAMA).

3 Requested listing

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

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Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Dispensed price for Max. Qty	Proprietary Name and Manufacturer	
BECLOMETASONE DIPROPIONATE +FORMOTEROL (EFORMOTEROL) FUMARATE, + GLYCOPYRRONIUM <i>beclometasone dipropionate 100 microgram/actuation + formoterol (eformoterol) fumarate dihydrate 6 microgram/actuation + glycopyrronium 10 microgram/actuation, 120 actuations</i>	NEW	1	1	5	\$ [REDACTED]	Trimbow	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 (CTO)
Restriction type / Method: <input checked="" type="checkbox"/> Authority Required – Streamlined [10167]
Administrative Advice: Continuing Therapy Only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.
Indication: Chronic obstructive pulmonary disease (COPD)
Treatment Phase: Initial and continuing [blank]
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, with significant symptoms despite regular bronchodilator therapy with a long acting muscarinic antagonist (LAMA) and a long acting beta-2 agonist (LABA) or an inhaled corticosteroid (ICS) and a LABA; OR Patient must have been stabilised on a combination of a LAMA, LABA and an ICS for this condition.
Administrative Advice: <i>Formal assessment and correction of inhaler technique should be performed in accordance with the COPD-X Plan (available at http://copdx.org.au/); the assessment and adherence to correct technique should be documented in the patient's medical records.</i>
Administrative Advice: Diagnosis of COPD should include measurement of airflow obstruction using spirometry, with confirmation of post-bronchodilator airflow obstruction.
Administrative Advice: This product is not PBS-subsidised for the treatment of asthma or the initiation of bronchodilator therapy in COPD.
Administrative Advice: The treatment must not be used in combination with an ICS/LABA, LABA/LAMA or LAMA, LABA or ICS monotherapy
Administrative Advice: A LAMA includes tiotropium, glycopyrronium, aclidinium or umeclidinium.
Administrative Advice: A LABA includes olodaterol, indacaterol, salmeterol, formoterol or vilanterol
Administrative Advice: An ICS includes fluticasone propionate, fluticasone furoate, budesonide, beclometasone or ciclesonide.

3.2 The ESC noted that the PBS clinical criteria are consistent with the TGA indication and with that of Trelegy Ellipta.

3.3 The requested PBS restriction for TRIMBOW did not include administrative advice related to the formal assessment and correct inhaler technique. The PBAC considered that this information should be included in the TRIMBOW restriction to be consistent with the current PBS restriction for Trelegy Ellipta.

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

4 Population and disease

- 4.1 COPD is a serious, progressive condition of non-reversible airflow obstruction, which mostly affects middle-aged and older people. The Australian Institute of Health and Welfare (AIHW) estimated that over 7,500 Australians (4,005 men and 3,513 women) died due to COPD in 2017, making it the fifth leading cause of death.¹
- 4.2 The COPD-X 2020 guidelines (p12) state the following with therapy increasing as disease severity increases until adequate control of breathlessness, improved functional capacity, and control of exacerbation frequency is achieved:
- Use short-acting inhaled bronchodilator therapy for short-term relief of breathlessness.
 - For patients receiving short-acting bronchodilators who have persistent troublesome dyspnoea, add a LAMA or LABA (or LABA/LAMA if monotherapy is not adequate) for regular use.
 - LAMA/LABA FDC in a single inhaler are available for patients who remain symptomatic despite monotherapy with either alone (GLY/indacaterol [IND], UMEC/VIL, tiotropium [TIO]/olodaterol [OLO] or acclidinium [ALC]/FOR).
 - Triple therapy (ICS/LABA/LAMA) should be limited to patients with repeated exacerbations and more severe COPD symptoms that cannot be adequately managed by dual therapy.
- 4.3 The target population considered in the submission is patients with moderate to severe COPD who are not adequately treated by a combination of an ICS and a LABA or a combination of a LABA and LAMA. The ESC considered that the positioning of TRIMBOW in the submission clinical algorithm aligns with the COPD-X guidelines.
- 4.4 The target population was well described and appropriate. The PBAC has previously seen the same population when considering the submission for Trelegy Ellipta².

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

5 Comparator

- 5.1 The submission nominated Trelegy Ellipta, a single inhaler triple therapy, as the main comparator.
- 5.2 Trelegy Ellipta is an appropriate comparator, given that it is PBS-listed for the same COPD target population, it is the only other single triple therapy available in Australia and is the medicine most likely to be displaced if TRIMBOW is approved. The ESC considered Trelegy Ellipta to be a reasonable comparator.

¹ <https://www.aihw.gov.au/getmedia/2ae179d3-180e-4f4a-9789-1a236da8b4bf/Chronic-obstructive-pulmonary-disease-COPD.pdf.aspx?inline=true>

² <https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2017-12/files/fluticasone-furoate-umeclidinium-vilanterol-psd-12-2017.pdf>

- 5.3 The submission acknowledged the concurrent administration of the individual components of TRIMBOW should also be considered as a comparator according to the PBAC Guidelines (Version 5.0). The submission argued this was not appropriate, as the use of three concurrent inhalers does not reflect standard medical practice for COPD, all restricted listings of BEC and FOR are for asthma only and where BEC does have an unrestricted listing it has very low utilisation for COPD.
- 5.4 In the evaluation of Trelegy Ellipta, the PBAC accepted that any combination of ICS/LABA/LAMA might be considered appropriate comparators and not those that specifically make up Trelegy Ellipta. The PBAC considered that LAMA/LABA dual therapy, and triple therapy via concomitant use of any combination of LAMA, LABA and ICS were appropriate (paragraph 7.3, Trelegy Ellipta, Public Summary Document, December 2017 PBAC meeting). There are a large number of ICS, LAMA and LABA products available alone or in various combinations on the PBS. The following combinations could be potentially considered as comparators for TRIMBOW: ICS/LABA + LAMA or LAMA/LABA + ICS.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from organisations (1) via the Consumer Comments facility on the PBS website. The comment from Lung Foundation Australia described a range of benefits of treatment with TRIMBOW including providing clinicians and patients with an additional choice of therapy that may encourage treatment adherence due to the three medicines being in one inhaler.

Clinical trials

- 6.3 The submission is based on three randomised trials comparing TRIMBOW to dual or open triple therapies. It also presented two randomised trials comparing Trelegy Ellipta to dual therapies. The clinical claim of non-inferiority in the effectiveness and safety of TRIMBOW versus Trelegy Ellipta was based on an indirect comparison of annual rates of moderate to severe COPD exacerbations.

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Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/Publication title	Publication citation
TRILOGY	Singh, D., et al. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β 2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial.	Lancet 2016; 388(10048); 963-973
TRINITY	Vestbo, J., et al. Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial.	Lancet 2017; 389(10082); 1919-1929
TRIBUTE	Papi, A., et al. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial.	Lancet 2018; 391(10125); 1076-1084
FULFIL	Lipson, DA. FULFIL Trial: Once-Daily Triple Therapy for Patients with Chronic Obstructive Pulmonary Disease.	American Journal of Respiratory and Critical Care Medicine 2017; 196(4); 438-446
IMPACT	Lipson, DA. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD.	The New England Journal of Medicine 2018; 378(18); 1671-1680

COPD: Chronic Obstructive Pulmonary Disease

Source: Compiled during the evaluation based on Section 2.2.6, pp34-35 of the submission

6.4 Table 3 summarises the key features of the randomised trials. The trials included patients with moderate to severe COPD.

Table 3: Key features of the included evidence

Trial	N	Design/duration (days ± SD) of treatment	Risk of bias	Patient population	Outcomes
TRIMBOW (BEC/FOR/GLY)					
TRILOGY	BEC/FOR/GLY n=687; BEC/FOR (ICS/LABA) n=680	MC, R, DB, parallel, 2w run- in + 52w treatment	Low	<ul style="list-style-type: none"> • ≥40 years • History of ≥1 moderate or severe COPD exacerbation in 12 months prior to screening • Functional symptoms assessed as CAT score > 10 • Current or former smoker • FEV1 <50% predicted normal, post-bronchodilator • FEV1/FVC ratio <0.7, post-bronchodilator • ICS+LABA, ICS+LAMA, LAMA+LABA or LAMA alone in 2 months prior 	<ul style="list-style-type: none"> • Change in Lung function (pre- and post-dose FEV1) (primary outcome) • Annual rate of COPD exacerbations over 52 weeks • Dyspnoea (primary outcome) • Change in SGRQ (total score and response) • Change in the use of rescue medication • Safety
TRINITY	BEC/FOR/GLY n=1077; TIO n=1076; BEC/FOR (ICS/LABA) +TIO n=537	MC, R, DB, parallel, 2 weeks run-in + 52w treatment	Low	<ul style="list-style-type: none"> • ≥40 years • History of ≥1 moderate or severe COPD exacerbation in 12 months prior to screening • Functional symptoms assessed as CAT score > 10 • Current or former smoker • FEV1 <50% predicted normal, post-bronchodilator • FEV1/FVC ratio <0.7, post-bronchodilator • ICS+LABA, ICS+LAMA, LAMA+LABA or LAMA alone in 2 months prior 	<ul style="list-style-type: none"> • Annual rate of COPD exacerbations over 52 weeks (primary outcome) • Change in lung function (pre- and post-dose FEV1) • Change in SGRQ (total score and response) • Change in the use of rescue medication • Safety
TRIBUTE	BEC/FOR/GLY n=764; IND+GLY (LABA/LAMA) n=768	MC, R, DB, parallel, 2 weeks run-in + 52w treatment	Low	<ul style="list-style-type: none"> • ≥40 years • History of ≥1 moderate or severe COPD exacerbation in 12 months prior to screening • Functional symptoms assessed as CAT score > 10 • Current or former smoker • FEV1 <50% predicted normal, post-bronchodilator • FEV1/FVC ratio <0.7, post-bronchodilator • ICS+LABA, ICS+LAMA, LAMA+LABA or LAMA alone in 2 months prior 	<ul style="list-style-type: none"> • Annual rate of COPD exacerbations over 52 weeks (primary outcome) • Change in lung function (pre- and post-dose FEV1) • Change in SGRQ (total score and response) • Change in the use of rescue medication • Safety

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TRELEGY ELIPTA (FLU/UMEC/VI)					
FULFIL	FF/UMEC/VI n=911; BUD/FOR (ICS/LABA) n= 899 [Until 24 weeks]; n=210 and n=220 respectively until 52 weeks	MC, R, DB, parallel, 2-weeks run-in + 24/52w treatment	Low	<ul style="list-style-type: none"> • ≥40 years • Current or former smoker • Functional symptoms assessed as CAT score ≥ 10 • FEV1 < 50% predicted normal post-bronchodilator OR • FEV1 < 80% predicted normal post-bronchodilator and either at least two moderate exacerbations or at least one severe exacerbation in the past year • Receiving daily maintenance therapy for COPD for at least 3 months (triple therapy allowed) • FEV1/FVC ratio <0.7, post-bronchodilator 	<ul style="list-style-type: none"> • Annual rate of COPD exacerbations at week 24 (extended until 52 weeks) • Change in trough FEV1 (co-primary outcome) • Change in SGRQ (total score and response) at week 24 (co-primary outcome) • Safety
IMPACT	FF/UMEC/VI n= 4151; FF/VI (ICS/LABA) n= 4134; VI/UMEC (LABA/LAMA) n=2070	MC, R, DB, parallel, 2-weeks run-in + 24/52w treatment	Low	<ul style="list-style-type: none"> • ≥40 years • Current or former smoker • Functional symptoms assessed as CAT score ≥ 10 • FEV1 < 50% predicted normal post-bronchodilator OR • FEV1 < 80% predicted normal post-bronchodilator and either at least two moderate exacerbations or at least one severe exacerbation in the past year • Receiving daily maintenance therapy for COPD for at least 3 months (triple therapy allowed) • FEV1/FVC ratio <0.7, post-bronchodilator 	<ul style="list-style-type: none"> • Annual rate of COPD exacerbations at week 52 (primary outcome) • Change in trough FEV1 • Change in SGRQ • Other outcomes • Safety

BD: Twice daily, BEC: Beclometasone, COPD: Chronic Obstructive Pulmonary Disease, D: once daily, DB: Double blind, FEV1: Forced expiratory flow in the first second of expiration; FF: Fluticasone furoate, FOR: Formoterol fumarate, FVC: Forced vital capacity, GLY: Glycopyrronium, ICS: Inhaled corticosteroids, IND: Indacaterol, LABA: Long-acting β-agonist, LAMA: Long-acting muscarinic antagonist, R: Randomised, SGRQ: St George Respiratory Questionnaire, TDI: Transition Dyspnoea Index, TIO: Tiotropium, UMEC: Umeclidinium, VI: Vilanterol

^a Including death from any cause during treatment, all exacerbations (mild, moderate, or severe), and dyspnoea according to the TDI. Source: Compiled based on section 2.4.1, p44 of the submission; Lipson et al. (2017)

6.5 The overall risk of bias in each of the individual randomised trials was low.

6.6 The indirect comparison involved the TRILOGY and TRIBUTE trials for TRIMBOW and the FULFIL and IMPACT trials for Trelegy Ellipta. TRINITY was excluded from the indirect analysis as it did not share a common comparator arm with either Trelegy Ellipta trial.

6.7 The ESC noted that the key differences in the patient baseline characteristics across the TRIMBOW and Trelegy Ellipta trials primarily related to the inclusion criteria:

- The inclusion criteria for the TRIMBOW trials required all patients to have experienced one moderate or severe COPD exacerbation in the year prior. However, at baseline a higher proportion of patients in the Trelegy Ellipta trials reported more than one COPD exacerbation in the year prior compared to the TRIMBOW trials (TRILOGY [n=1367] 19.8% experienced > 1 COPD exacerbation, TRIBUTE [n=1532] 19.2%, FULFIL [n=1810] 37.3%, IMPACT [n=10,355] 54.6%)
- The inclusion criteria for the TRIMBOW trials required that all patients had a FEV1 < 50% predicted normal post-bronchodilator, whereas the Trelegy Ellipta trials allowed an FEV1 > 80% predicted normal post-bronchodilator if patients had also experienced at least 1 severe or 2 moderate COPD exacerbations in the past year. The mean FEV1 predicted normal values were lower in the TRIMBOW trials (TRILOGY 36.5%, TRIBUTE 36.4%) than the Trelegy Ellipta trials (FULFIL 45.3%, IMPACT 45.5%).
- The TRIMBOW trials excluded patients who had received prior triple therapy. In contrast, 32% to 40% of patients in the Trelegy Ellipta trials had received prior triple therapy.³

6.8 The specific LABA/LAMA treatments differed between the TRIMBOW and the Trelegy Ellipta trials:

- IND/GLY (i.e. Ultibro®) in TRIBUTE;
- VIL/UMEK (i.e. Anoro® Ellipta®) in IMPACT.

The specific ICS/LABA treatments also differed between the TRIMBOW and Trelegy Ellipta trials:

- BEC/FOR (i.e. Fostair®) in TRILOGY;
- FF/VIL (i.e. Breo® Ellipta®) in IMPACT;
- Budesonide (BUD)/FOR (i.e. Symbicort® Turbuhaler®) in FULFIL.

The differences in the common comparators for the TRIMBOW and Trelegy Ellipta trials added uncertainty to the results from the indirect comparisons. The Pre-Sub-Committee response (PSCR) argued that while specific comparator treatments differed, comparisons were made using common comparators from the same class of drugs. The PSCR also argued that in the evaluation of Trelegy Ellipta, the PBAC accepted that any fixed combination of ICS/LABA/LAMA, LAMA/LABA, or any combination of ICS, LABA, and LAMA are appropriate comparators. The PSCR stated that this suggests a level of interchangeability between products of the same class. The ESC noted that while BEC/FOR (Fostair) is TGA indicated for the symptomatic

³ Langham S, et.al. Single-inhaler triple therapy in patients with chronic obstructive pulmonary disease: a systematic review. Respiratory Research 2019; 20:242. <https://doi.org/10.1186/s12931-019-1213-9>

treatment of adults with severe COPD and a history of repeated exacerbations it is not PBS listed for this indication.

- 6.9 The annual rate of COPD exacerbations was the only outcome used in the indirect comparison. It was a secondary outcome for TRILOGY and FULFIL, while the other trials included it as a primary or co-primary outcome.
- 6.10 The submission included only a subset of FULFIL (n=430 patients) in the indirect comparison because data related to the annual rate of COPD exacerbations was collected only on that subset at 52 weeks. While the submission considered this subsample as a randomised subset of the total trial population, the patient baseline characteristics of the subset were not provided.
- 6.11 In the assessment of Trelegy Ellipta, the PBAC considered indirect comparisons on a range of outcomes, COPD exacerbations, lung function tests, dyspnoea, quality of life (i.e. St George Respiratory Questionnaire (SGRQ)) and rescue medication use, to determine non-inferiority between Trelegy Ellipta and its comparators (paragraph 6.8, Trelegy Ellipta Public Summary Document (PSD), December 2017 PBAC meeting). By contrast, the current submission presented indirect comparisons on only COPD exacerbation rates. The ESC agreed with the PSCR that the transitivity issues raised increased the uncertainty of the indirect comparison.
- 6.12 The submission did not nominate a minimal clinically important difference (MCID) for the outcome of COPD exacerbation rates. The PSCR reiterated that this is consistent with the PBAC submission for Trelegy Ellipta, which also did not present a MCID for this outcome (paragraph 6.21, Trelegy Ellipta PSD, December 2017 PBAC meeting). In addition, the PSCR stated that a non-inferiority margin was not defined in a systematic review of exacerbation outcomes in trials of all single-inhaler triple therapies.⁴ Likewise, the PSCR argued that a non-inferiority margin was not defined for annual rate of COPD exacerbations between TRIMBOW and the open triple therapy (Fostair + tiotropium) in the TRINITY study.

Comparative effectiveness

- 6.13 Table 4 summarises results related to moderate and severe COPD exacerbations over 52 weeks reported in TRILOGY, TRINITY and TRIBUTE. In TRILOGY, the rate of moderate and severe exacerbations was significantly reduced by 23% with TRIMBOW compared with BEC/FOR (Fostair) ($p=0.005$). In TRINITY, TRIMBOW reduced the rate of moderate and severe exacerbations by 20% compared with TIO monotherapy ($p=0.003$). However, there were no significant differences in moderate to severe COPD exacerbations between TRIMBOW and Fostair + TIO in TRINITY. In TRIBUTE, the difference in exacerbation rate was reduced by 15% in favour of TRIMBOW, when compared to IND/GLY (Ultibro) ($p=0.043$).

⁴ Langham S, et.al. Single-inhaler triple therapy in patients with chronic obstructive pulmonary disease: a systematic review. Respiratory Research 2019; 20:242. <https://doi.org/10.1186/s12931-019-1213-9>

- 6.14 While the submission did not present a MCID for COPD exacerbations, Calverley (2005) suggested that a 20% reduction in moderate or severe exacerbations would constitute a MCID. This MCID has also been assumed by the European Public Assessment Report for TRIMBOW. If this MCID is assumed to be relevant, the reduction in moderate and moderate to severe COPD exacerbations over 52 weeks with TRIMBOW compared with Fostair and with TIO could be clinically important, whereas that with Fostair + TIO triple therapy and Ultibro dual therapy may not be clinically important.

Table 4: Moderate and severe COPD exacerbations over 52 weeks– ITT population

	TRILOGY ^a		TRINITY ^b			TRIBUTE ^b	
	TRIMBOW	Fostair	TRIMBOW	TIO	Fostair+TIO	TRIMBOW	Ultibro
	n=687	n=680	n=1012	n=1005	n=512	n=764	n=768
Patients with exacerbations, n (%)	214 (31.1)	240 (35.3)	351 (32.6)	383 (35.7)	167 (31.0)	273 (35.7)	288 (37.5)
Number of exacerbations	288	353	485	569	244	433	485
Exacerbation rate per patient per year	0.448	0.565	0.472	0.583	0.474	0.603	0.686
Adjusted Exacerbation Rate per patient per year (95% CI)	0.410 (0.358; 0.469)	0.530 (0.468; 0.600)	0.457	0.571	0.452	0.504 (0.447, 0.569)	0.595 (0.530, 0.668)
Adjusted rate ratio (95% CI) ^c	0.773 (0.647; 0.924)			0.801 (0.693; 0.925)	1.013 (0.846; 1.214)	0.848 (0.723, 0.995)	
P-value ^c	0.005			0.003	0.887	0.043	

CI: Confidence Interval, GLY=Glycopyrronium, TIO=Tiotropium. Bold text indicates statistical significance at p<0.05

^a COPD exacerbation was a secondary outcome

^b COPD exacerbation rate was a primary outcome

^c TRIMBOW vs TIO in TRINITY

^d TRIMBOW vs Fostair + TIO in TRINITY

^e Fostair + TIO vs TIO in TRINITY

Source: Compiled during the evaluation based on Tables 41-43, pp81-83 of the submission

- 6.15 Table 5 summarises results related to the mean change from baseline in lung function in terms of pre-dose morning forced expiratory volume in one second (litre) [FEV1 (L)].
- 6.16 TRIMBOW led to a statistically significant mean change in pre-dose morning FEV1 (L) compared with Fostair in TRILOGY and TIO in TRINITY. However, the mean changes in pre-dose FEV1 were not statistically significant for TRIMBOW compared with Fostair + TIO in TRINITY or Ultibro in TRIBUTE. The proportion of responders (i.e. those reaching the MCID of ≥ 0.1 L) at 52 weeks was also significantly higher for TRIMBOW vs Fostair in TRILOGY and for TRIMBOW vs TIO in TRINITY.
- 6.17 The adjusted mean differences for all comparisons related to pre-dose FEV1 were statistically significant but below the specified MCID of 0.1L. Thus, it is uncertain if the gains from TRIMBOW are clinically meaningful.

Table 5: Change from baseline in pre-dose morning FEV1 (L) at all weeks; FEV1 response

TRILOGY			TRINITY					TRIBUTE			
W	Adj. mean (95% CI)		Adj. mean diff (95% CI)	Adj mean (95% CI)			Adj. mean diff (95% CI)		Adj. mean (95% CI)		Adj. mean diff (95% CI)
	TRIM	Fostair		TRIM	TIO	Fostair + TIO	TRIM vs TIO	TRIM vs Fostair + TIO	TRIM	Ultibro	
Change from baseline											
12	0.078 (0.060, 0.096)	0.010 (-0.008, 0.028)	0.068 (0.042 , 0.094)	0.082 (0.066, 0.097)	0.030 (0.015, 0.046)	0.101 (0.080, 0.123)	0.051 (0.029 , 0.073)	-0.020 (-0.046, 0.007)	0.019 (0.003, 0.034)	-0.013 (0.028, 0.003)	0.032 (0.010 , 0.054)
26	0.082 (0.062, 0.102)	0.001 (-0.019, 0.021)	0.081 (0.052 , 0.109)	0.075 (0.059, 0.092)	0.024 (0.007, 0.041)	0.086 (0.063, 0.109)	0.051 (0.028 , 0.075)	-0.011 (-0.039, 0.018)	-0.015 (-0.031, 0.001)	-0.034 (-0.050, -0.018)	0.020 (-0.003, 0.042)
52	0.071 (0.050, 0.093)	0.008 (-0.014, 0.030)	0.063 (0.032 , 0.094)	0.082 (0.065, 0.100)	0.021 (0.003, 0.039)	0.085 (0.061, 0.110)	0.061 (0.037 , 0.086)	-0.003 (-0.033, 0.027)	-0.029 (-0.046, -0.012)	-0.049 (-0.066, -0.031)	0.019 (-0.005, 0.043)
Average pre-dose FEV1 over 52 weeks											
52	0.084 (0.067, 0.100)	0.012 (-0.005, 0.029)	0.072 (0.048 , 0.096)	0.080 (0.067, 0.093)	0.022 (0.009, 0.036)	0.091 (0.073, 0.110)	0.058 (0.039 , 0.077)	-0.011 (-0.034, 0.012)	-0.003 (-0.016, 0.010)	-0.026 (-0.039, -0.013)	0.022 (0.004 , 0.040)
Responders^a, n (%) and odds ratio instead of the adjusted mean and adjusted mean difference											
W	TRIM, n(%)	Fostair, n(%)	OR	TRIM, n(%)	TIO, n(%)	Fostair + TIO, n(%)	TRIM vs TIO OR	TRIM vs Fostair + TIO, OR	TRIM, n(%)	Ultibro, n(%)	OR
26	287 (41.8)	165 (24.3)	2.299 (1.817 , 2.910)	421 (39.1)	306 (28.5)	204 (37.9)	1.61 (1.34 , 1.93)	1.04 (0.84, 1.30)	176 (23.0)	156 (20.3)	1.176 (0.921, 1.503)
52	259 (37.7)	158 (23.2)	2.061 (1.621 , 2.620)	408 (37.9)	295 (27.5)	210 (39.0)	1.62 (1.35 , 1.95)	0.95 (0.76, 1.18)	145 (19.0)	125 (16.3)	1.190 (0.913, 1.550)

CI: Confidence Interval, FEV: Forced expiratory volume, OR = odds ratio, TIO: Tiotropium, TRIM: TRIMBOW W: Weeks

^a A patient was classified as a non-responder if the change from baseline was <100 mL or if pre-dose morning FEV1 was missing.

Bold indicates statistically significant results; Bold adjusted mean differences in TRILOGY and TRIBUTE were all statistically significant at p<0.001, whereas bold adjusted mean differences were significant at p<0.05 in TRIBUTE.

Source: Compiled during the evaluation based on Tables 44, 46, 47, pp84, 86-87, 90 of the submission

6.18 In TRILOGY, the adjusted mean change from baseline in 2-hour post-dose FEV1 was significantly greater in the TRIMBOW group, ranging from 0.215–0.268L with TRIMBOW versus 0.138–0.153L with Fostair (all p<0.001). At 26 weeks, 2-hour post-dose FEV1 improved more with TRIMBOW than with Fostair, with a statistically significant difference between the groups (adjusted mean difference: 0.11L, 95% CI: 0.086L, 0.147L, p<0.001). In TRIBUTE, changes from baseline in post-dose FEV1 between treatment groups were mostly not significant, with the exception of that in week 40 (results not presented in Table 5), which was in favour of TRIMBOW (adjusted mean difference: 0.055, 95% CI: 0.010, 0.100 p=0.017).

6.19 Table 6 presents results related to change from baseline Transition Dyspnoea Index (TDI) focal score (a measure of dyspnoea) at week 4, 12, 26, 40 and 52, and TDI

response at weeks 26 and 52. Only TRILOGY reported TDI results among TRIMBOW trials.

- 6.20 At the 26-week measure, treatment with TRIMBOW did not result in a significantly improved TDI focal score compared with Fostair (adjusted mean difference: 0.21, p=0.160) although there were more responders, i.e. those reaching a MCID of ≥ 1 (p= 0.027).

Table 6: TRILOGY primary and secondary endpoints – change from baseline in TDI focal score at week 26; TDI focal score at other weeks; TDI response at weeks 26 and 52

Weeks	Adjusted mean, TRIMBOW (n=687)	Adjusted mean, Fostair (n=680)	Adjusted mean difference	P-value
Change from baseline				
4	1.54 (1.35; 1.72)	1.12 (0.94; 1.31)	0.41 (0.15; 0.68)	0.002
12	1.77 (1.58; 1.97)	1.39 (1.19; 1.58)	0.38 (0.11; 0.66)	0.007
26	1.71 (1.50; 1.92)	1.50 (1.29; 1.71)	0.21 (-0.08; 0.51)	0.160
40	1.80 (1.58; 2.01)	1.65 (1.43; 1.86)	0.15 (-0.16; 0.45)	0.343
52	2.03 (1.81; 2.25)	1.81 (1.59; 2.04)	0.21 (-0.10; 0.53)	0.186
Responders^a, n (%) and odds ratio presented instead of the adjusted mean and adjusted mean difference				
26	394 (57.4)	352 (51.8)	1.280 (1.029; 1.594)	0.027
52	370 (53.9)	354 (52.1)	1.093 (0.877; 1.362)	0.43

TDI: Transition Dyspnoea Index

^a patient was classed as a non-responder if the TDI focal score change from baseline did not reach the MCID of ≥ 1 .

Bold p-values indicate statistically significant results

Source: Compiled during the evaluation based on Table 49, pp91-92 of the submission

- 6.21 Table 7 presents the change in SGRQ total score from baseline to weeks 26 and 52 and SGRQ responders (i.e. reduction in SGRQ by ≥ 4 units) at weeks 26 and 52.
- 6.22 Patients treated with TRIMBOW had statistically significant SGRQ total score compared with Fostair at 52 weeks in TRILOGY (adjusted mean difference: -1.69, p= 0.029) and TIO in TRINITY (-1.60, p= 0.010). Furthermore, TRIMBOW led to more responders at both 26 and 52 weeks when compared with Fostair as well as TIO. Both comparisons were statistically significant. TRIMBOW did not result in statistically significant results for either measure (or at either time point) when compared with Fostair + TIO in TRINITY.
- 6.23 The gains from TRIMBOW were less than the nominated MCID (i.e. 4 point decrease in SGRQ score) in the submission, and therefore not clinically important.

Table 7: Change from baseline in SGRQ total score at weeks 26 and 52; SGRQ responders at weeks 26 and 52

W	TRILOGY			TRINITY					TRIBUTE		
	Adj. Mean (95% CI)		Adj. Mean diff (95% CI)	Adj. Mean (95% CI)			Adj. Mean diff (95% CI)		Adj. Mean (95% CI)		Adj. Mean diff (95% CI)
	TRIM	Fostair		TRIM	TIO	Fostair + TIO	TRIM vs TIO	TRIM vs Fostair + TIO	TRIM	Ultibro	
Change from baseline											
26	-4.76 (-5.69, -3.83)	-3.43 (-4.38, -2.47)	-1.33 (-2.66, 0.01)	-5.44 (6.26, -4.62)	-4.41 (-5.24, -3.59)	-7.20 (-8.35, -6.05)	-1.03 (-2.19, 0.14)	1.76 (0.35, 3.17)	NA	NA	NA
52	-5.12 (-6.18, -4.06)	-3.43 (-4.51, -2.35)	-1.69 (-3.20, -0.17)	-5.74 (-6.60, -4.88)	-4.14 (-5.01, -3.27)	-7.32 (-8.51, -6.12)	-1.60 (-2.82, -0.38)	1.57 (0.10, 3.05)	-3.20 (-3.81, -2.58)	-1.52 (-2.13, -0.90)	-1.68 (-2.55, -0.81)
Responders^a, n (%) and odds ratio instead of the adjusted mean and adjusted mean difference											
26	321 (46.7)	246 (36.2)	1.521 (1.211, 1.911)	508 (47.2)	438 (40.8)	276 (51.3)	1.32 (1.10, 1.57)	0.81 (0.65, 1.00)	NA	NA	NA
52	297 (43.2)	244 (35.9)	1.327 (1.060, 1.661)	494 (45.9)	423 (39.4)	254 (47.2)	1.33 (1.11, 1.59)	0.91 (0.73, 1.13)	NA	NA	NA

Adj: Adjusted, CI: Confidence Interval, NA: Not Available, TIO: Tiotropium, W: Weeks

^a Patient was classed as a non-responder if the SGRQ total score change from baseline did not reach the MCID of ≥ 4 (decrease of 4 or more units).

Bold adjusted mean differences indicate statistically significant results.

Source: Compiled based on Tables 50, 51, 52, pp93, 94-95, 96 of the submission

- 6.24 In TRILOGY, TRIMBOW led to a significant change in the percentage of days without rescue medication as well as total puffs per day until week 26 compared with treatment with Fostair. However, TRIMBOW did not improve total puffs per day at week 52 (adjusted mean difference: 2.65, 95% CI: -0.14, 5.45, $p=0.063$). In TRINITY, patients treated with TRIMBOW had statistically significant results in terms of percentage of days without the use of rescue medication and in total puffs per day over 52 weeks (both $p<0.001$). There were no statistically significant differences in the average use of rescue medication between the TRIMBOW group and the Fostair + TIO group for any of the inter-visit periods. Similarly, there was no statistically significant difference between TRIMBOW and Ultibro in any measure of rescue medication use in TRIBUTE. This implies that TRIMBOW is unlikely to improve the percentage of days without the use of rescue medication and total puffs per day compared with an open-triple therapy (Fostair + TIO) or Ultibro.
- 6.25 The ESC considered that TRIMBOW appeared efficacious compared with Fostair and TIO monotherapy. However, the average improvement was above the MCID proposed for the outcome of COPD exacerbation only. In terms of Fostair + TIO and Ultibro monotherapy, for all outcomes where an average improvement was reported the difference was less than the proposed MCID.
- 6.26 The submission conducted three separate indirect comparisons between TRIMBOW and Trelegy Ellipta on the annual rate of moderate to severe COPD exacerbations. The common comparator (LABA/LAMA or ICS/LABA) and time point for the measurement of exacerbations in FULFIL (24 or 52 weeks) differed across the comparisons.

6.27 The results of the indirect analyses for exacerbation rates are presented in Table 8. Indirect rate ratios >1 in Table 8 denote higher (worse) exacerbation rates for TRIMBOW compared to Trelegy Ellipta. The indirect comparison rate ratio of 1.13 (0.95, 1.34) for the comparison of TRIBUTE vs IMPACT was validated as part of this review. However, it was not possible to validate the two rate ratios for the comparison of TRILOGY vs IMPACT+FULFIL during the evaluation, as the submission did not present the methodology of the calculation.

Table 8: Results of indirect analysis of exacerbation outcomes in comparable TRIMBOW and Trelegy Ellipta trials

Annual rate of moderate to severe COPD exacerbations	Common comparator	Indirect Rate Ratio (95% CI)	p-value
TRIBUTE vs IMPACT	LABA/LAMA	1.13 (0.95, 1.34)	0.158
TRILOGY vs IMPACT+FULFIL (annualised rate at 52 weeks on subgroup for FULFIL)	ICS/LABA	1.06 (0.69, 1.64)	0.781
TRILOGY vs IMPACT+FULFIL (annualised rate at 24 weeks on full population for FULFIL)	ICS/LABA	1.00 (0.74, 1.37)	0.987

ICS: Inhaled corticosteroids, LABA: Long-acting β -agonist, LAMA: Long-acting muscarinic antagonist

The indirect rate ratios and p-values are correct.

Source: Table 66, p114 of the submission

6.28 The ESC considered that the key differences between the TRIMBOW and Trelegy Ellipta trials outlined in paragraph 6.7 and 6.8 add uncertainty to the results from the indirect comparisons of COPD exacerbation rates.

6.29 The ESC noted that for the first comparison, with common comparator LABA/LAMA, the upper 95% confidence interval (CI) is 1.34. The upper 95% CIs for the two comparisons using ICS/LABA as the common comparator are 1.64 and 1.37. The submission did not nominate a non-inferiority margin. The lack of a statistically significant difference between treatments is not a robust methodology for determining non-inferiority and may not adequately justify the claim of similar efficacy given the wide confidence intervals for the annual rate of moderate to severe COPD exacerbations outcomes, which indicate substantial uncertainty around the indirect estimate of effects.

Comparative harms

6.30 The submission presented safety outcomes to the end of the treatment phases of the key TRIMBOW trials: TRILOGY, TRINITY and TRIBUTE. The incidence of adverse events (AEs) were similar between treatment arms in all three trials.

6.31 There were no significant safety issues identified for TRIMBOW in TRILOGY, TRINITY, and TRIBUTE. The incidence of pneumonia was slightly higher in the TRIMBOW arm in TRILOGY, TRINITY and TRIBUTE. None of the deaths reported was considered to be related to study medication.

- 6.32 Overall, the incidence of AEs in both Trelegy Ellipta trials (IMPACT and FULFIL) were similar between treatment arms. Therefore, the ESC considered it reasonable to conclude that the safety profiles of TRIMBOW and Trelegy Ellipta are similar.

Benefits/harms

- 6.33 A benefits/harms analysis was not presented as the clinical claim is of non-inferiority.

Clinical claim

- 6.34 Based on results from pivotal trials TRILOGY, TRINITY and TRIBUTE, the submission claimed that TRIMBOW has:

- Superior efficacy compared with Fostair (i.e. ICS/LABA) and TIO monotherapy (i.e. LAMA).
- Non-inferior efficacy compared with Fostair + TIO (i.e. ICS/LABA+LAMA) administered concomitantly.
- Non-inferior safety compared with Fostair, Fostair + TIO and TIO monotherapy.

- 6.35 The submission claimed that TRIMBOW is non-inferior in terms of effectiveness and safety compared with Trelegy Ellipta. The claim of non-inferior efficacy for TRIMBOW vs Trelegy Ellipta was uncertain due to:

- An indirect comparison being performed for annual COPD exacerbation rates only. The PBAC submission of Trelegy Ellipta considered additional clinical outcomes.
- For the indirect comparisons of exacerbation rates, the upper 95% confidence intervals were 1.34, 1.64 and 1.37. The submission did not nominate a non-inferiority margin. The PSCR argued that is consistent with the PBAC submission for Trelegy Ellipta, which also did not present a MCID for this outcome. The ESC considered the wide confidence intervals indicated substantial uncertainty around the indirect estimate of effects.
- There were some differences in patient baseline characteristics, and the specific LABA/LAMA and ICS/LABA treatments, between the TRIMBOW and Trelegy Ellipta trials. The PSCR argued that comparisons were made across common comparators in the same class of drugs. The pre-PBAC response further argued that previous rulings by the PBAC support the conclusion that any fixed combinations of ICS, LAMA and LABA drugs can be considered equivalent for the purposes of comparator analysis.

- 6.36 The PBAC considered that the claim of non-inferior comparative effectiveness was uncertain but reasonable.

- 6.37 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

- 6.38 The submission presented a cost-minimisation analysis based on ‘costs per year’ between TRIMBOW and Trelegy Ellipta. The costs per year were estimated as the product of the DPMQ and number of packs per year. The analysis assumed no additional costs or cost-offsets.
- 6.39 The submission proposed the following equi-effective doses based on the trial evidence presented:
- TRIMBOW (BEC/FOR/GLY) 100mcg/6mcg/10mcg two actuations twice daily = Trelegy Ellipta (FF/UMEC/VI) 100mcg /62.5mcg /25mcg one actuation once daily.
- 6.40 The dosing of TRIMBOW is the same in both pivotal trials and the Product Information of TRIMBOW.
- 6.41 Based on the cost-minimisation analysis presented in the submission the requested price for TRIMBOW was the same as for Trelegy Ellipta (AEMP = \$76.78).
- 6.42 In the PSD of Trelegy Ellipta, the PBAC had stated that ‘the ceiling price of Trelegy (or any other fixed combination of triple therapy of LAMA/LABA/ICS) should be no greater than the lowest priced combination of any listed components of the triple therapy’ (paragraphs 7.6 to 7.8, Trelegy Ellipta PSD, December 2017 PBAC meeting). Of the TRIMBOW components, BEC 100 mcg (Qvar100) and GLY are PBS-listed for COPD, whereas all PBS listings of FOR are for asthma only.
- 6.43 As outlined in paragraph 5.4, in the evaluation of Trelegy Ellipta, the PBAC accepted that any combination of ICS/LABA/LAMA might be considered appropriate comparators and not those that specifically make up Trelegy Ellipta. Under Section 101(3B) of the *National Health Act 1953*, the PBAC cannot recommend listing a therapy at a price that is substantially more costly than an alternative therapy unless it is satisfied that the therapy provides, for some patients, a significant improvement in efficacy or reduction in toxicity. Based on the same principle, the ceiling price for any fixed combination of triple therapy of ICS/LABA/LAMA should be no greater than the lowest price combination of any listed components of triple therapy (i.e. ICS/LABA + LAMA or LAMA/LABA + ICS).
- 6.44 The lowest cost ICS/LABA + LAMA combination is FF/VI 100/25 mcg (AEMP \$41.88) plus TIO 18 mcg (AEMP \$28.82) with a cost of \$70.70. The lowest cost LAMA/LABA + ICS combination is TIO/OLO 2.5/2.5 mcg (AEMP \$57.27) plus FF 100 mcg (AEMP \$15.65) with a cost of \$72.92. These are lower than the AEMP of Trelegy Ellipta (\$76.78) and the proposed AEMP for TRIMBOW. The PSCR argued that the FF 100 mcg component of the lowest cost LAMA/LABA + ICS combination is not appropriate as the TGA approved Product Information lists asthma as its indication for use. The pre-PBAC response noted the sponsor would consider alternative combinations for calculating the price of TRIMBOW and proposed fluticasone/salmeterol 250/50 mcg with TIO 18 mcg as appropriate in this context with

a cost of \$75.60. The PBAC noted the ICS/LABA + LAMA combination selected by the sponsor was not the lowest cost combination.

- 6.45 The ESC noted that in the evaluation of Trelegy Ellipta the PBAC considered that, based on the assessment of benefits and harms of triple therapy with Trelegy Ellipta over LAMA/LABA dual therapy, any improvement in efficacy should be balanced against the increased harms from prolonged ICS exposure in COPD patients. Under Section 101(3B) of the National Health Act 1953, in December 2017 the PBAC was satisfied that, for some patients, there was a significant improvement in efficacy sufficient to justify that triple therapy with Trelegy Ellipta could be more costly than the alternative therapy, LAMA/LABA. As such, the PBAC advised that a small price advantage could be negotiated for Trelegy Ellipta over the price of a currently listed LAMA/LABA FDC to reflect this likely small improvement in efficacy and unquantified increase in toxicity (paragraph 7.7, Trelegy Ellipta PSD, December 2017 PBAC meeting).

Drug cost/patient/year

- 6.46 The annual cost of TRIMBOW is \$ [REDACTED] per patient, based on the proposed DPMQ of \$ [REDACTED] and 12.175 scripts per year.

Estimated PBS usage & financial implications

- 6.47 The submission was not considered by DUSC.
- 6.48 The estimated financial impact of the proposed listing of TRIMBOW for COPD on the PBS used a market share approach and assumed that TRIMBOW would be a single alternative inhaler ICS/LABA/LAMA triple therapy alongside Trelegy Ellipta.
- 6.49 Table 9 summarises the key inputs used in the financial estimates.

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Table 9: Data sources and parameter values applied in the utilisation and financial estimates

Parameter	Input	Source/Notes
COPD market growth rate without Trelegy Ellipta from 2015 - 2019	-5.16%	PBS services data http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp
PBS services	PBS services for the 2019 calendar year for comparator item codes. PBS: 283,226 RPBS: 9,705 Total: 292,931	http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp
Trelegy Ellipta market growth rate	2020 – 25% 2021 – 40% 2022 – 23% 2023 – 12% 2024 – 11% 2025 – 4% 2026 – 4%	PBS services data http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp ; Sponsor projections
TRIMBOW rate of displacement	2021 – 7% 2022 – 20% 2023 – 27% 2024 – 31% 2025 – 31% 2026 – 31%	Symbicort Australian launch analogue
Unit equivalence between TRIMBOW and Trelegy Ellipta	1:1	
TRIMBOW, BEC/ FOR/GLY	Ex-manufacturer price (\$AUD) - \$76.78, DPMQ (\$AUD) - \$94.57	Proposed price
Trelegy Ellipta, FF/UMEC/VI	Ex-manufacturer price (\$AUD) - \$■■■■, DPMQ (\$AUD) - \$■■■■	PBS Schedule

BEC=Beclometasone; FF: Fluticasone furoate, FOR=Formoterol, GLY=glycopyrronium, UMEC: Umeclidinium, VI: Vilanterol
Source: Table 78, pp131-132 of the submission

6.50 Table 10 summarises the estimated use and financial impact of the requested listing of TRIMBOW.

Table 10: Estimated use and financial implications to the PBS/RPBS

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimation of use and financial impact of the proposed medicine on PBS/RPBS						
TRIMBOW						
Total units	1	2	2	3	3	3
PBS/RPBS cost	\$ 4	\$ 5	\$ 5	\$ 6	\$ 6	\$ 6
PBS/RPBS net cost (less copay)	\$ 4	\$ 5	\$ 5	\$ 5	\$ 6	\$ 6
Estimation of changes in use and financial impact of comparators						
Trelegy Ellipta						
Total units	1	2	2	3	3	3
PBS/RPBS cost	-\$ 8	-\$ 8	-\$ 8	-\$ 8	-\$ 8	-\$ 8
PBS/RPBS net cost (less copay)	-\$ 8	-\$ 8	-\$ 8	-\$ 8	-\$ 8	-\$ 8
Estimated financial implications for the PBS/RPBS						
Net cost of new listing	\$ 4	\$ 5	\$ 5	\$ 5	\$ 6	\$ 6
Net cost of changed listing	-\$ 8	-\$ 8	-\$ 8	-\$ 8	-\$ 8	-\$ 8
PBS/RPBS net cost (less copay)	\$ 7	\$ 7	\$ 7	\$ 7	\$ 7	\$ 7
Estimated financial implications for the Health Budget						
Net change in PBS	\$ 7	\$ 7	\$ 7	\$ 7	\$ 7	\$ 7
Net change in RPBS	\$ 7	\$ 7	\$ 7	\$ 7	\$ 7	\$ 7
Total net change in health budget	\$ 7	\$ 7	\$ 7	\$ 7	\$ 7	\$ 7

¹Units' refer to number of PBS/RPBS services

Abbreviations: PBS: Pharmaceutical Benefits Scheme, RPBS: Repatriation Schedule of Pharmaceutical Benefits

Source: Table 81, p135; Table 83, p136; Table 84-86, pp137-138, Table 88, pp138-139 of the submission

The redacted values correspond to the following ranges:

¹30,000 to <40,000

²100,000 to <200,000

³200,000 to <300,000

⁴\$0 to <\$10 million

⁵\$10 million to <\$20 million

⁶\$20 million to <\$30 million

⁷<500

⁸net cost saving

6.51 At the requested price (DPMQ=\$⁴), the proposed listing of TRIMBOW was estimated to result in a total cost to the PBS/RPBS of \$90 million to < \$100 million over the first six years of listing, net of co-payments. However, this cost would be offset by a net cost saving of \$90 million to < \$100 million due to the proportional decline in the use of Trelegy Ellipta.

6.52 The PBAC noted that the financial estimates would need to be recalculated to take into account the outcome of its considerations regarding the cost-minimisation analysis.

Quality Use of Medicines

6.53 The submission stated that the sponsor would take necessary measures to ensure the quality use of TRIMBOW by:

- Providing materials regarding the appropriate dosing with TRIMBOW
- Providing education for physicians and nurse practitioners on the approved dosing schedules for TRIMBOW.

- 6.54 Given the number and complexity of respiratory devices currently available in Australia, a significant education program may be required to ensure consumers use TRIMBOW safely and appropriately.
- 6.55 Education programs may also be required to prevent the potential for early dose escalation, which could happen as a result of movement from dual to triple therapy earlier than required in the treatment algorithm.

Financial Management – Risk Sharing Arrangements

- 6.56 No risk sharing arrangement was proposed for TRIMBOW. The PBAC previously considered a risk-sharing arrangement for Trelegy Ellipta appropriate to address concerns raised about underestimated market share and market growth, as well as quality use of medicines issues identified in relation to use earlier in the treatment pathway than clinically appropriate (paragraph 6.64, Trelegy Ellipta PSD, December 2017 PBAC meeting). The PSCR stated that the sponsor is open to discussions with the PBAC regarding a potential risk-sharing arrangement for TRIMBOW if it receives a positive recommendation for listing.

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

7 PBAC outcome

- 7.1 The PBAC recommended the Authority Required (STREAMLINED) listing of the fixed dose combination (FDC) of beclometasone (BEC) with formoterol (FOR) and glycopyrronium (GLY), TRIMBOW, for maintenance treatment of moderate to severe chronic obstructive pulmonary disease (COPD) that is not adequately treated by a combination of an inhaled corticosteroid (ICS) with long-acting beta2-agonist (LABA) or LABA with a long-acting muscarinic antagonist (LAMA).
- 7.2 The PBAC considered that the claim of non-inferior effectiveness and safety to the FDC of fluticasone furoate (FF), umeclidinium (UMEC) and vilanterol (VIL), Trelegy Ellipta, was reasonable. However, the PBAC considered for the purposes of satisfying Section 101(3B) of the *National Health Act 1953*, both Trelegy Ellipta, as well as any triple combination therapy via concomitant use of a LAMA, LABA and ICS are relevant alternative therapies. The PBAC's recommendation was therefore, among other matters, based on its assessment that the cost of TRIMBOW should be no greater than the lowest price combination of the PBS listed components of the triple therapy that are available for COPD, and that TRIMBOW should be subject to the same risk sharing arrangements as are currently in place for Trelegy Ellipta.
- 7.3 The PBAC noted the input from Lung Foundation Australia supporting the listing of TRIMBOW for maintenance treatment of COPD.
- 7.4 The PBAC considered Trelegy Ellipta to be an appropriate comparator. In addition, the PBAC also considered that triple therapy via concomitant use of any combination of LAMA, LABA and ICS were appropriate alternative therapies.

- 7.5 The PBAC noted that the claim of non-inferior effectiveness for TRIMBOW versus Trelegy Ellipta was based on an indirect comparison of annual COPD exacerbation rates. The PBAC noted that, like the Trelegy Ellipta submission in December 2017, a minimal clinically important difference (MCID) was not nominated for this outcome. The PBAC noted the differences in the patient baseline characteristics, and the specific LABA/LAMA and ICS/LABA treatments, between the TRIMBOW and Trelegy Ellipta trials (see paragraphs 6.7 and 6.8). The PBAC agreed with the sponsor that the Committee's acceptance of any combination of LAMA, LABA and ICS as appropriate comparators supports a level of interchangeability between products of the same class. Overall, the PBAC considered that the claim of non-inferior comparative effectiveness was uncertain but reasonable.
- 7.6 The PBAC considered that the claim of non-inferior comparative safety was reasonable.
- 7.7 The PBAC noted that the submission presented a cost-minimisation analysis between TRIMBOW and Trelegy Ellipta and accepted the following equi-effective doses as the basis for the analysis:
- TRIMBOW (BEC/FOR/GLY) 100mcg/6mcg/10mcg two actuations twice daily = Trelegy Ellipta (FF/UMEC/VI) 100mcg/62.5mcg/25mcg one actuation once daily.
- However, as outlined in paragraph 7.4, the PBAC considered that triple therapy via concomitant use of any combination of LAMA, LABA and ICS were appropriate alternative therapies. Under Section 101(3B) of the *National Health Act 1953*, the PBAC cannot recommend listing a therapy at a price that is substantially more costly than an alternative therapy unless it is satisfied that the therapy provides, for some patients, a significant improvement in efficacy or reduction in toxicity. Based on the same principle, the PBAC considered that the ceiling price for any fixed combination of triple therapy of ICS/LABA/LAMA should be no greater than the lowest price combination of any listed components of COPD triple therapy. The PBAC noted that the AEMP for TRIMBOW would be lower than the current AEMP for Trelegy Ellipta (see paragraph 6.44) due to price reductions that have occurred for some components over time.
- 7.8 The PBAC considered that, while the AEMP for TRIMBOW would be lower than that of Trelegy Ellipta, the two products were considered non-inferior and anticipated to substitute in the COPD market. The PBAC also recalled that at its December 2017 meeting that Trelegy Ellipta would be acceptably cost-effective if its price was not substantially greater than the price of LAMA/LABA dual therapy and recommended that a small price advantage be negotiated over the price of currently listed LAMA/LABA FDCs (paragraph 7.1, Trelegy Ellipta PSD, December 2017 PBAC meeting). As such, the PBAC considered it appropriate that TRIMBOW be subject to the same risk sharing arrangements currently in place for Trelegy Ellipta.
- 7.9 The PBAC considered that should the sponsor of TRIMBOW offer a lower price in line with the intent of the December 2017 Trelegy Ellipta recommendation, while ensuring

it does not exceed the ceiling price criteria set out in paragraph 7.7, then risk sharing arrangements for TRIMBOW would not be required.

- 7.10 The PBAC noted the financial estimates would need to be recalculated to take into account the outcome of its considerations regarding the cost-minimisation analysis.
- 7.11 The PBAC advised that under Section 101(3BA) of the *National Health Act 1953* TRIMBOW should be treated as interchangeable on an individual patient basis with Trelegy Ellipta.
- 7.12 The PBAC advised that TRIMBOW is suitable for prescribing by nurse practitioners.
- 7.13 The PBAC recommended that the Early Supply Rule should apply to TRIMBOW.
- 7.14 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because TRIMBOW is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over Trelegy Ellipta, 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.
- 7.15 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 medicinal product with the same restriction as the combination product fluticasone furoate + umeclidinium + vilanterol (restriction summary 10166; Trelegy Ellipta); as follows:

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
BECLOMETASONE + FORMOTEROL (EFORMOTEROL) + GLYCOPYRRONIUM					
beclometasone dipropionate 100 microgram/actuation + formoterol (eformoterol) fumarate dihydrate 6 microgram/actuation + glycopyrronium 10 microgram/actuation, 120 actuations	NEW	1	1	5	Trimbow
Restriction Summary 10166/ Treatment of Concept: 10167					
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners (CTO)					
Restriction type: <input checked="" type="checkbox"/> Authority Required – Streamlined [10167]					
Administrative Advice: Formal assessment and correction of inhaler technique should be performed in accordance with the COPD-X Plan (available at http://copdx.org.au/); the assessment and adherence to correct technique should be documented in the patient's medical records.					
Administrative Advice: Diagnosis of COPD should include measurement of airflow obstruction using spirometry, with confirmation of post-bronchodilator airflow obstruction.					
Administrative Advice: This product is not PBS-subsidised for the treatment of asthma or the initiation of bronchodilator therapy in COPD.					
Administrative Advice: The treatment must not be used in combination with an ICS/LABA, LABA/LAMA or LAMA, LABA or ICS monotherapy.					
Administrative Advice: A LAMA includes tiotropium, glycopyrronium, aclidinium or umeclidinium.					
Administrative Advice: A LABA includes olodaterol, indacaterol, salmeterol, formoterol or vilanterol.					
Administrative Advice: An ICS includes fluticasone propionate, fluticasone furoate, budesonide, beclometasone or ciclesonide.					
Administrative Advice: Continuing Therapy Only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.					
Indication: Chronic obstructive pulmonary disease (COPD)					
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, with significant symptoms despite regular bronchodilator therapy with a long acting muscarinic antagonist (LAMA) and a long acting beta-2 agonist (LABA) or an inhaled corticosteroid (ICS) and a LABA; OR					
Patient must have been stabilised on a combination of a LAMA, LABA and an ICS for this condition.					

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

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available

through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

Chiesi Australia welcomes the PBAC decision to list TRIMBOW® on the PBS for maintenance treatment of moderate to severe chronic obstructive pulmonary disease (COPD) and will work with the PBAC to ensure timely access for patients.