

## 5.08 TEZACAFTOR with IVACAFTOR, Pack containing tezacaftor 100 mg with ivacaftor 150 mg tablets and ivacaftor 150 mg tablets, Symdeko<sup>®</sup>, Vertex Pharmaceuticals

Note: The submission provided by the sponsor contained information relevant to two different patient groups and proposed PBS listings: cystic fibrosis patients who are homozygous for the F508 deletion and those with residual function (RF) mutations. For clarity, two separate Public Summary Documents (PSDs) have been presented. This PSD deals with the evidence for patients who are homozygous for the F508del mutation in the CFTR gene.

### 1 Purpose of Application

1.1 The submission presented an application for Section 100 (Highly Specialised Drugs Program) listing for tezacaftor 100 mg with ivacaftor 150 mg in a fixed dose combination (tezacaftor/ivacaftor) for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation in the CF transmembrane conductance regulator (CFTR) gene. The key components of the submission are presented in Table 1. Tezacaftor/ivacaftor had not been previously considered by the PBAC.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	CF patients aged 12 years and older: PBS listing for tezacaftor/ivacaftor in patients who are homozygous for the <i>F508del</i> mutation.
Intervention	One tablet containing tezacaftor 100 mg/ivacaftor 150 mg in the morning and one tablet containing ivacaftor 150 mg in the evening, approximately 12 hours apart.
Comparator	Lumacaftor/ivacaftor for patients who are homozygous for the F508del-CFTR mutation.
Outcomes	Primary outcome: <ul style="list-style-type: none"> <li>Absolute change from baseline in ppFEV<sub>1</sub>.</li> </ul> Secondary outcomes: <ul style="list-style-type: none"> <li>Relative change from baseline in ppFEV<sub>1</sub>.</li> <li>Pulmonary exacerbation measures.</li> <li>Absolute change from baseline in nutritional status (body mass index (BMI), BMI-for-age z-score, body weight, body weight-for-age z-score, height-for-age z-score).</li> <li>Absolute change from baseline in the CFQ-R Respiratory Domain Score.</li> </ul>
Clinical Claim	Tezacaftor/ivacaftor plus BSC is non-inferior in terms of efficacy and safety compared to lumacaftor/ivacaftor plus BSC.

Abbreviations: BMI=body mass index; BSC=best supportive care; CF=cystic fibrosis; CFQ-R=Cystic Fibrosis Questionnaire-Revised; CFTR=cystic fibrosis transmembrane conductance regulator; PBS=Pharmaceutical Benefits Scheme; ppFEV=percent predicted forced expiratory volume.

Source: Table 1.1.1, page 34 of the Submission.

### 2 Requested listing

2.1 The requested restriction is summarised in Table 2.

**Table 2: Details of the proposed listing**

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
TEZACAFTOR/IVACAFTOR (SYMDEKO®) Pack containing tezacaftor 100 mg/ivacaftor 150 mg tablets and ivacaftor 150 mg tablets.	1	5	\$21,000	Symdeko®,	Vertex
Category/Program:	Section 100 - Highly Specialised Drugs Program – Authority Required				
Treatment criteria:	Must be treated by a specialist respiratory physician with expertise in cystic fibrosis, OR Must be treated in consultation with a specialist respiratory physician with expertise in cystic fibrosis if attendance is not possible due to geographic isolation; AND Must be treated in a centre with expertise in cystic fibrosis, OR Must be treated in consultation with a centre with expertise in cystic fibrosis if attendance is not possible due to geographic isolation.				
Clinical criteria:	Patient must be homozygous for the <i>F508del</i> mutation on the <i>CFTR</i> gene AND The treatment must be a sole PBS-subsidised disease-modifying therapy for this condition, AND The treatment must be given concomitantly with standard therapy for this condition.				
Population criteria:	Patients must be 12 years or older.				

Abbreviations: CF= cystic fibrosis; CFTR: Cystic fibrosis transmembrane conductance regulator; FEV1: forced expiratory volume in one second; RF= residual function

Sources: Table 1.4.2, p58 of the submission

- 2.2 The requested basis for listing is cost-minimisation compared with lumacaftor/ivacaftor. However, the proposed DPMQ (of \$21,000) is higher than that for lumacaftor 100 mg/ivacaftor 125 mg at \$18,750 (public hospital DPMQ); both are for 28-day supplies.
- 2.3 The submission did not request a Special Pricing Arrangement in the form of a published versus an effective price. Instead, the submission proposed a reduction in the estimated gross cost of tezacaftor/ivacaftor via a subsidisation cap, to be implemented through the current Risk Sharing Arrangement (RSA) for lumacaftor/ivacaftor. While the submission stated that the intent of the proposed RSA was to achieve a price of \$ [REDACTED] per patient per year, the ESC noted there was a significant risk that the Government would pay a higher amount per patient (see *Financial Management – Risk Sharing Arrangements* section for further details).
- 2.4 The ESC considered it would be appropriate to include prescribing instructions specifying that the dosage of tezacaftor/ivacaftor should be adjusted if the patient is concomitantly receiving a moderate or strong CYP3A inhibitor. The draft Product Information specifies that patients concomitantly receiving moderate CYP3A inhibitors should be dosed with tezacaftor 100 mg/ivacaftor 150 mg and ivacaftor 150 mg tablets on alternate days, while patients concomitantly receiving strong CYP3A inhibitors should be dosed with tezacaftor 100 mg/ivacaftor 150 mg twice weekly (approximately 3 to 4 days apart). The ESC noted that similar prescribing instructions are included in the current listings of ivacaftor.

- 2.5 The PBAC also noted that the TGA approved Product Information states that concomitant use of CYP3A inducers may result in reduced efficacy and that co-administration with strong CYP3A inducers is not recommended.

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

### 3 Background

#### **Registration status**

- 3.1 **TGA status at time of PBAC consideration:** The submission was made under the TGA/PBAC Parallel Process. At the time of evaluation for PBAC consideration, the TGA Clinical Evaluation Report – Round 2 was available. No major efficacy or safety issues were raised by the clinical evaluator. The TGA Delegates Overview and Minutes of the ACM meeting on 6 December 2018 were available at the time of ESC consideration. Tezacaftor/ivacaftor was registered by the TGA on 5 March 2019.
- 3.2 The TGA approved indications are: *Symdeko is indicated for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence. Refer to Table 1 [of the TGA approved Product Information] for a list of responsive mutations.*

### 4 Population and disease

- 4.1 CF is a rare, genetic, systemic disease that leads to early death. It is caused by mutations in the CFTR gene which ultimately lead to defective transport of chloride and other ions. Patients that suffer CF are subject to a progressive loss of lung function, significant excess morbidity and reduced quality of life, pancreatic insufficiency and gastrointestinal malabsorption, frequent pulmonary exacerbations, and premature death. In Australia, the median age of death among CF patients is 32.6 years (Australian Cystic Fibrosis Data Registry (ACFDR) annual report, 2016).
- 4.2 The most common mutation in Australia is F508del of the CFTR, which is present in at least one allele in approximately 90% of CF patients. Approximately 50% of CF patients in Australia are homozygous for (i.e. have two copies of) the F508del mutation. The F508del mutation leads to an improperly folded CFTR protein and a disruption of the chloride channel opening leading to minimal CFTR chloride transport activity. Other mutations may cause a reduced synthesis or stability of the CFTR protein which may result in retention of residual activity and therefore, less severe disease.

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

## 5 Comparator

- 5.1 The submission nominated lumacaftor/ivacaftor as the main comparator as it is listed on the PBS for use in the same patient population. The ESC considered this was appropriate.

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

## 6 Consideration of the evidence

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician indicated that despite lumacaftor/ivacaftor being an effective treatment for many patients with CF, there remains a clinical need for other treatment options such as tezacaftor/ivacaftor. The clinician discussed the differences between the treatment profiles of tezacaftor/ivacaftor and lumacaftor/ivacaftor in particular, emphasising that tezacaftor/ivacaftor was associated with fewer drug-drug interactions. The clinician noted that treatment with lumacaftor/ivacaftor may be stopped due to contraindications to concomitant use with drugs such as antibiotics, hormonal contraceptives and antidepressants. The clinician claimed that the significant difference in absolute change in FEV<sub>1</sub> compared with baseline (1.59%, 95% CI: 0.17, 3.01) in patients treated with tezacaftor/ivacaftor in the indirect comparison against lumacaftor/ivacaftor was clinically important. The clinician emphasised the importance of the rate of pulmonary exacerbations as a predictor of long-term survival and decline in lung function noting that tezacaftor/ivacaftor was associated with a smaller number of pulmonary exacerbations in the indirect comparison against lumacaftor/ivacaftor.
- 6.2 In response to a question from the PBAC regarding whether clinicians were likely to switch all patients from lumacaftor/ivacaftor to tezacaftor/ivacaftor, the clinician indicated that patients experiencing AEs or who are on medications for which concomitant administration with lumacaftor/ivacaftor is contraindicated and who have suboptimal lung function results on lumacaftor/ivacaftor would be switched to tezacaftor/ivacaftor. The clinician stated that patients who were stable on treatment with lumacaftor/ivacaftor would be unlikely to be switched to tezacaftor/ivacaftor in the short-term but that there may be an adverse event or drug interaction that would eventually trigger a switch to tezacaftor/ivacaftor.
- 6.3 In response to a question from the PBAC regarding why uptake of lumacaftor/ivacaftor has so far been lower than expected, the clinician explained that initiating patients on treatment with lumacaftor/ivacaftor requires significant resources, including, for some, admission to hospital and treatments with antibiotics and oral corticosteroids, which is a limiting factor in the rate of patient initiation. The clinician further explained that a number of patients require treatment and hospitalisation prior to initiating lumacaftor/ivacaftor due to the high risk of initial worsening of symptoms among

patients initiated with FEV<sub>1</sub> < 50%. The clinician claimed that most major treatment centres in Australia were following a clinical protocol which required patients to be stabilised prior to lumacaftor/ivacaftor treatment. The PBAC considered that the hearing was informative as it provided insight on the current use of lumacaftor/ivacaftor (including the clinical protocol for initiating treatment), as well as how tezacaftor/ivacaftor would be used, in clinical practice.

### ***Consumer comments***

- 6.4 The PBAC noted and welcomed the input from individuals (137), health professionals (2) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described the potential treatment benefits of tezacaftor/ivacaftor and emphasised the importance of additional CFTR modulator treatment options for patients who do not respond to, are contraindicated to, or experience side effects on, treatment with lumacaftor/ivacaftor. The comments also indicated that many patients perceived tezacaftor/ivacaftor to be more effective at slowing the progression of illness (including in terms of lung function) than lumacaftor/ivacaftor.
- 6.5 Cystic Fibrosis Australia (CFA) indicated support for tezacaftor/ivacaftor to be listed on the PBS noting the fewer drug-drug interactions associated with this treatment compared to lumacaftor/ivacaftor. CFA and Cystic Fibrosis Tasmania (CFTAS) noted that many patients with CF also experience depression and anxiety and emphasised the positive impact that treatment would have on patients' mental health.

### ***Clinical trials***

- 6.6 The submission was based on an indirect treatment comparison (ITC) of tezacaftor/ivacaftor and lumacaftor/ivacaftor. The ITC included three, phase III randomised controlled trials (two comparing lumacaftor/ivacaftor versus BSC; TRAFFIC and TRANSPORT, N=739, including a pooled analysis of those studies) and one comparing tezacaftor/ivacaftor versus BSC (EVOLVE, N=504). The extension study for lumacaftor/ivacaftor (PROGRESS) was not considered by the submission for the assessment of comparative clinical evidence.
- 6.7 Details of the trials presented in the submission are provided in Table 3.

**Table 3: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
EVOLVE Study 106	A phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of VX-661 in combination with ivacaftor in subjects aged 12 years and older with cystic fibrosis, homozygous for the <i>F508del-CFTR</i> mutation. 12 June 2018.	Clinical Study Report Study VX14-661-106
	A randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of VX-661 in combination with ivacaftor. <a href="https://clinicaltrials.gov/ct2/show/NCT02347657">https://clinicaltrials.gov/ct2/show/NCT02347657</a>	ClinicalTrials.gov Identifier NCT02347657
	Taylor-Cousar JL, Munck A, McKone EF, <i>et al.</i> Tezacaftor–ivacaftor in patients with cystic fibrosis homozygous for <i>Phe508del</i> .	<i>New England Journal of Medicine</i> ; 2017; 337:2013-2023.
	Taylor-Cousar JL, Lekstrom-Himes J, Wang L, Lu Y, Elborn S. Efficacy and safety of tezacaftor/ ivacaftor in patients aged >=12 years with CF homozygous for <i>F508del-CFTR</i> : A randomized placebo-controlled phase 3 trial.	<i>Pediatric Pulmonology</i> ; 2017; 52(Suppl 47): 307.
	Taylor-Cousar JI ES. Advances in treating patients homozygous for <i>F508del</i> .	<i>Pediatric pulmonology</i> ; 2017; 52(Suppl 47): 173.
	Sutharsan S, Taylor-Cousar J, Lekstrom-Himes J, <i>et al.</i> Efficacy and safety of tezacaftor/ivacaftor in patients aged >= 12 years with CF homozygous for <i>F508del-CFTR</i> : A randomized placebo (PBO)-controlled phase 3 trial.	<i>Pneumologie</i> ; 2018; 72(Suppl 1): S36.
Study 110 VX14-661-110	Flume PA, Owen CA, Brown CD, <i>et al.</i> Long-term safety and efficacy of tezacaftor/ivacaftor in patients with cystic fibrosis homozygous for <i>F508del-CFTR</i> or heterozygous for <i>F508del</i> and a RF mutation: First interim analysis results of a phase 3, open-label, rollover study.	American journal of respiratory and critical care medicine 2018; 197(Meeting Abstracts): A7807
TRAFFIC VX12-809-103	Study to evaluate safety, efficacy and tolerability of TEZ/IVA in patients with cystic fibrosis (CF) who have previously discontinued Orkambi.	2017
	A phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the <i>F508del-CFTR</i> Mutation.	Clinical study report VX12-809-103 08 September 2014.
	A study in people with cystic fibrosis (a rare hereditary pulmonary disease) to assess the efficacy and safety of a combination of two experimental drugs.	EUCTR 2012-003989-40 2013
	Elborn J, Wainwright CE, Ramsay B, Huang X, <i>et al.</i> Effect of lumacaftor in combination with ivacaftor in patients with cystic fibrosis who are homozygous for <i>F508del-CFTR</i> : The traffic study.	<i>Pediatric Pulmonology</i> ; 2014; 49: 304
TRANSPORT VX12-809-104	A phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the <i>F508del-CFTR</i> Mutation.	Clinical study report VX12-809-104 (NCT01807949) 02 September 2014
	Wainwright CE, Elborn JS, Ramsey B, Marigowda G <i>et al.</i> Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for <i>Phe508del</i> <i>CFTR</i> .	<i>New England Journal of Medicine</i> ; 2015; 373:220-23.
	Ramsay B, Boyle MP, Elborn J, Huang X, <i>et al.</i> Effect of lumacaftor in combination with ivacaftor in patients with cystic fibrosis who are homozygous for <i>F508del-CFTR</i> : Transport study.	<i>Pediatric Pulmonary</i> ; 2014; 49: 305
Pooled analysis of TRAFFIC and TRANSPORT	De Boeck K, Elborn J, Ramsey B, Boyle MP, <i>et al.</i> Efficacy and safety of lumacaftor+ivacaftor combination therapy in patients with CF homozygous for <i>F508del-CFTR</i> by FEV <sub>1</sub> subgroups.	<i>Pediatric Pulmonary</i> ; 2015; 50:283.
	Elborn JS, Ramsey B, Boyle MP, Wainwright C, <i>et al.</i> Lumacaftor/ivacaftor combination therapy in CF patients homozygous for <i>F508del-CFTR</i> with severe lung dysfunction.	<i>Journal of Cystic Fibrosis</i> ; 2015; 14: S94.

Trial ID	Protocol title/ Publication title	Publication citation
	Elborn JS, Ramsey B, Boyle MP, Wainwright C, <i>et al.</i> Lumacaftor in combination with ivacaftor in patients with cystic fibrosis who are homozygous for the <i>F508del-CFTR</i> mutation.	<i>Journal of Cystic Fibrosis</i> ; 2015; 14: S1.
	Elborn JS, Ramsey B, Boyle MP, Konstan MW, <i>et al.</i> Efficacy and safety of lumacaftor/ivacaftor combination therapy in patients with cystic fibrosis homozygous for <i>Phe508del-CFTR</i> by pulmonary function subgroup: a pooled analysis.	<i>The Lancet Respiratory Medicine</i> ; 2016; 4(8): 617
	Solem CT, Vera-Llonch M, Tai M and O'Callaghan L. Pulmonary exacerbations, lung dysfunction, and EQ-5D measures in adolescents and adults with cystic fibrosis and homozygous for the <i>F508del-CFTR</i> mutation.	<i>Value in Health</i> ; 2016; 19(3): A116–A117.
	Sullivan JC, Accurso FJ, Marigowda G, Beusmans J, <i>et al.</i> Combination lumacaftor/ivacaftor therapy improves inflammatory biomarkers in patients with CF homozygous for the <i>F508del-CFTR</i> mutation.	<i>Pediatric Pulmonary</i> ; 2016; 51:274.
	Wainwright CE, Elborn JS, Ramsey B, Huang X, <i>et al.</i> Effect of lumacaftor in combination with ivacaftor in patients with CF who are homozygous for <i>DeltaF508-CFTR</i> : Phase 3 TRAFFIC and TRANSPORT studies.	<i>Pediatric Pulmonology</i> ; 2014; 49(Suppl 38): 156–157.

Abbreviations: CF=cystic fibrosis; CFTR= cystic Fibrosis transmembrane conductance regulator.

Source: Table 2.1.4, p.67-68 and Table 2.1.5, p. 69-70 of the Submission

6.8 The key features of the direct randomised trials are summarised in Table 4.

**Table 4: Key features of the included evidence – indirect comparison**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
<b>Tezacaftor/ivacaftor vs. placebo</b>					
EVOLVE	510	R, DB, MC 24 weeks	Low	CF patients aged 12 years and older who are homozygous for the <i>F508del</i> mutation in the <i>CFTR</i> gene.	Absolute change from baseline at Week 24 in ppFEV <sub>1</sub>
<b>Lumacaftor/ivacaftor vs. placebo</b>					
TRAFFIC	559	R, DB, MC 24 weeks	Low	CF patients aged 12 years and older who are homozygous for the <i>F508del</i> mutation in the <i>CFTR</i> gene.	Absolute change from baseline at Week 24 in ppFEV <sub>1</sub>
TRANSPORT	563	R, DB, MC 24 weeks	Low	CF patients aged 12 years and older who are homozygous for the <i>F508del</i> mutation in the <i>CFTR</i> gene.	Absolute change from baseline at Week 24 in ppFEV <sub>1</sub>

Abbreviations: CF=cystic fibrosis; CFTR=cystic fibrosis transmembrane conductance regulator DB=double blind; MC=multi-centre; NA=not applicable, OL=open label; ppFEV<sub>1</sub>= percent predicted forced expiratory volume in one second; R=randomised.

Source: Compiled during the evaluation.

### **Comparative effectiveness**

6.9 The submission presented an ITC of the primary and secondary outcomes in EVOLVE with the pooled results from TRAFFIC and TRANSPORT to compare tezacaftor/ivacaftor to lumacaftor/ivacaftor with placebo as the common comparator, applying the Bucher method for analysis.

6.10 The primary efficacy outcome in EVOLVE, TRAFFIC and TRANSPORT was the absolute change in in ppFEV<sub>1</sub> from baseline to Week 24. The results of the ITC (see Table 5)

show the absolute change in ppFEV<sub>1</sub> achieved with tezacaftor/ivacaftor was 1.59% (95% CI: 0.17, 3.01; p=0.028) greater than that observed with lumacaftor/ivacaftor. The relative change in ppFEV<sub>1</sub> at Week 24 using a mixed-effects model for repeated measures (MMRM) analysis, was a difference of 3.19% (95% CI: 0.44, 5.94; p=0.0231) for tezacaftor/ivacaftor compared with lumacaftor/ivacaftor. There was no statistically significant difference between treatments in terms of the number of pulmonary exacerbations nor the absolute change in BMI from baseline.

**Table 5: Results of the ITC of tezacaftor/ivacaftor and lumacaftor/ivacaftor at Week 24<sup>a</sup>**

Trial	Tezacaftor/ivacaftor	Common reference Placebo	Comparator Lumacaftor/ivacaftor	Measure of Effect (95% CI)
<b>Absolute change from baseline in ppFEV<sub>1</sub> at Week 24, LSM (SE)</b>				
EVOLVE	3.6 (0.4)	-0.8 (0.4)	-	4.4 (3.3, 5.4)
TRAFFIC and TRANSPORT		-0.32 (0.376)	2.49 (0.379)	2.81 (1.80, 3.82)
Indirect estimate of effect adjusted for the common reference (LSM)				<b>1.59 (0.17, 3.01) p=0.028</b>
<b>Relative change from baseline in ppFEV<sub>1</sub> at Week 24, LSM (SE)</b>				
EVOLVE	6.4 (0.8)	-1.6 (0.8)	-	8.0 (5.9, 10.1)
TRAFFIC and TRANSPORT		-1.09 (0.08)	4.64 (0.666)	4.81 (3.03, 6.59)
Indirect estimate of effect adjusted for the common reference (LSM)				<b>3.19 (0.44, 5.94) p=0.0231</b>
<b>Number of PExs through Week 24, Number of events (event per patient per year)</b>				
EVOLVE	78/248 (31%)	122/256 (48%)	-	0.65 (0.48, 0.88) <sup>b</sup>
TRAFFIC and TRANSPORT	-	251/371 (68%)	152/369 (41%)	0.61 (0.49, 0.76) <sup>b</sup>
Indirect estimate of effect adjusted for the common reference (RR)				1.066 (0.733, 1.549) p= 0.7395
<b>Number of PExs requiring IV antibiotic and/or hospitalisation through Week 24, Number of events (event per patient per year)</b>				
EVOLVE	39/248 (16%)	74/256 (29%)		0.53 (0.34, 0.82) <sup>b</sup>
TRAFFIC and TRANSPORT		149/371 (40%)	81/369 (22%)	0.44 (0.33, 0.60) <sup>b</sup>
Indirect estimate of effect adjusted for the common reference (RR)				1.20 (0.70, 2.04) p=0.504
<b>Absolute change from baseline in BMI from baseline at Week 24, LSM (SE)</b>				
EVOLVE	0.18 (0.05)	0.12 (0.05)	-	0.06 (0.07) (-0.08, 0.19)
TRAFFIC and TRANSPORT	-	0.13 (0.05)	0.37 (0.05)	0.24 (0.07) (0.11, 0.37)
Indirect estimate of effect adjusted for the common reference (LSM)				-0.18 (-0.37, 0.01) p=0.062

Abbreviations: BMI=body mass index; CI=confidence interval; IV=intravenous, LSM=least square mean; N=number; PEx= pulmonary exacerbation; ppFEV<sub>1</sub>=percent predicted forced expiratory volume in one second; RR=relative risk; SD=standard deviation; SE=standard error

Notes: <sup>a</sup> Conducted by averaging the mean absolute change at Week 16 and Week 24.

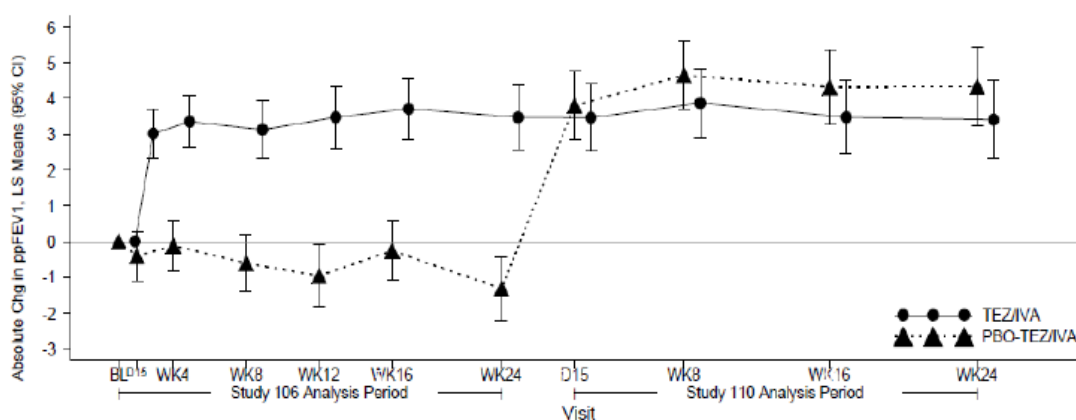
<sup>b</sup> RR (95% CI)

Statistically significant differences indicated in bold.

Source: Table 2.6.1 and Table 2.6.2 of the Commentary

6.11 The Pre-Sub-Committee Response (PSCR) presented updated data from extension Study 110 from a recent interim analysis of the 24-week follow-up visit (i.e. up to 48 weeks of treatment, including 24 weeks in EVOLVE) – see Figure 1.

Figure 1: MMRM analysis of the absolute change from baseline in ppFEV<sub>1</sub> at each visit, Study 106 (EVOLVE) FAS and Study 106/110 Efficacy Set



Abbreviations: BL= baseline; D= day; FEV= forced expiratory volume; IVA= ivacaftor; MMRM= mixed-effects model for repeated measures; PBO= placebo; TEZ= tezacaftor; WK= week  
Source: PSCR

- 6.12 The PSCR noted that the absolute change from baseline in ppFEV<sub>1</sub> was maintained through week 24 of Study 110. The PSCR further noted that the LS mean absolute change from baseline in ppFEV<sub>1</sub> was 3.4% (95% CI 2.3, 2.5) in the tezacaftor/ivacaftor group.
- 6.13 The ESC considered that while the Study 110 interim analysis data appeared to support the maintenance of treatment effect beyond 24 weeks (up to 48 weeks), the long-term efficacy of tezacaftor/ivacaftor in this patient population remains unknown.

### Comparative harms

- 6.14 Based on the ITC, the submission concluded that both tezacaftor/ivacaftor and lumacaftor/ivacaftor are well-tolerated with overall adverse event (AE) rates similar to those for placebo.
- 6.15 The results of the ITC between tezacaftor/ivacaftor and lumacaftor/ivacaftor for any AEs, related AEs, SAEs, related SAEs and AEs leading to discontinuation were not statistically significantly different between the treatments (see Table 6). There were fewer treatment-related AEs for tezacaftor/ivacaftor compared with lumacaftor/ivacaftor (RR 0.676; 95% CI: 0.481, 0.949; p=0.0239). The submission stated that the results of the ITC were directionally in favour of tezacaftor/ivacaftor with the exception of SAEs, the analysis of which was based on a very small number of events.

**Table 6: Indirect comparison of tezacaftor/ivacaftor and lumacaftor/ivacaftor for overall AE outcomes**

Trial type or estimate	Tezacaftor/ivacaftor, n with event/N (%)	Comparator Lumacaftor/ivacaftor, n with event/N (%)	Common reference, n with event/N (%)	RR (95% CI)
<b>Any AEs</b>				
EVOLVE	227/251 (90.4)		245/258 (95.0)	0.95 (0.91, 1.00)
TRAFFIC and TRANSPORT		351/369 (95.1)	355/370 (95.9)	0.99 (0.96, 1.02)
Indirect estimate of effect adjusted for the common reference			0.960 (0.904, 1.018); p=0.173	
<b>Treatment-related AE</b>				
EVOLVE	64/251 (25.5)		66/258 (25.6)	1.00 (0.74, 1.34)
TRAFFIC and TRANSPORT		191/369 (51.8)	129/370 (34.9)	1.48 (1.25, 1.76)
Indirect estimate of effect adjusted for the common reference			<b>0.676 (0.481, 0.949); p=0.0239</b>	
<b>SAEs</b>				
EVOLVE	31/251 (12.4)		47/258 (18.2)	0.68 (0.45, 1.03)
TRAFFIC and TRANSPORT		64/369 (17.3)	106/370 (28.6)	0.61 (0.46, 0.80)
Indirect estimate of effect adjusted for the common reference			1.115 (0.679, 1.830); p=0.668	
<b>Treatment-related SAEs</b>				
EVOLVE	5/251 (2.0)		3/258 (1.2)	1.71 (0.41, 7.09)
TRAFFIC and TRANSPORT		14/369 (3.8)	8/370 (2.2)	1.75 (0.75, 4.13)
Indirect estimate of effect adjusted for the common reference			0.977 (0.186, 5.146); p=0.978	
<b>AEs leading to discontinuations</b>				
EVOLVE	7/251 (2.8)		8/258 (3.1)	0.90 (0.33, 2.44)
TRAFFIC and TRANSPORT		17/369 (4.6)	6/370 (1.6)	2.84 (1.13, 7.13)
Indirect estimate of effect adjusted for the common reference			0.317 (0.082, 1.231); p=0.097	

Abbreviations: AEs=adverse events; CI=confidence interval; N/n=number; RR=risk ratio or relative risk; SAEs=serious adverse events

Note: Statistically significant differences indicated in bold

Source: Table 2.6.3 of the Commentary

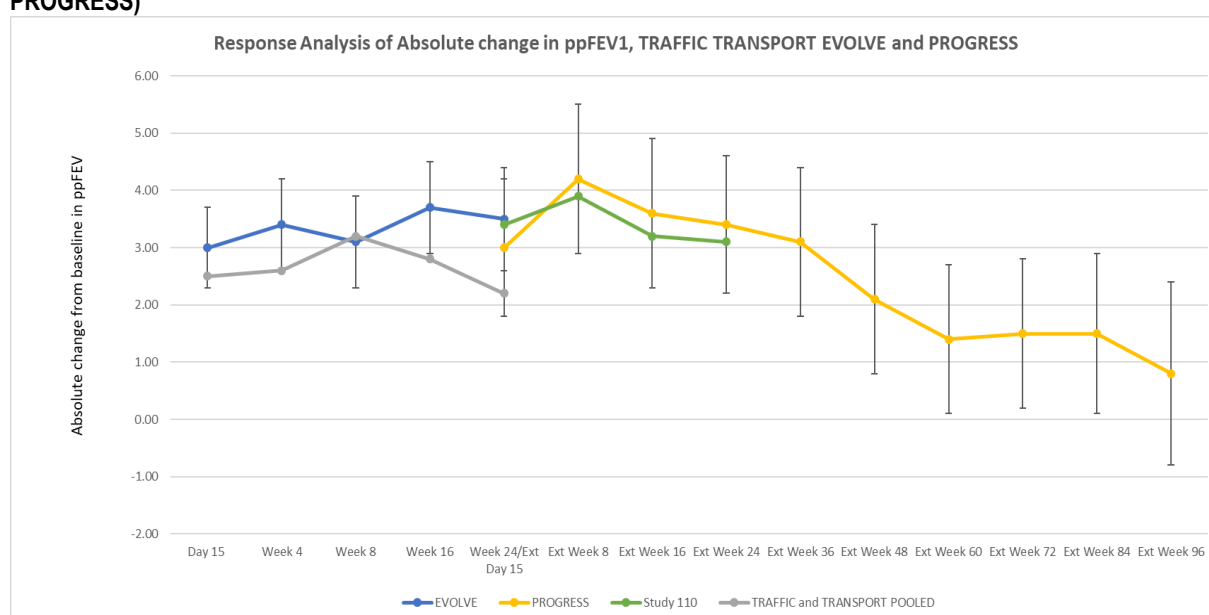
6.16 Based on the results presented by the submission the rates of respiratory events considered as part of the safety events were higher for lumacaftor/ivacaftor vs. placebo and comparable between tezacaftor/ivacaftor vs. placebo. Overall, the comparisons of safety may be confounded by small event numbers and the inclusion of CF symptoms (e.g. cough) as AEs.

### **Clinical claim**

6.17 The submission described tezacaftor/ivacaftor as at least non-inferior, if not superior, to lumacaftor/ivacaftor in terms of lung function improvement. The submission did not nominate a minimum clinically important difference (MCID) for ppFEV<sub>1</sub>. The submission argued that, in the context of an indirect comparison, it would not be appropriate to set a non-inferiority margin based on a benchmark MCID for improvement in ppFEV<sub>1</sub>, when the objective of treatment is stabilisation in lung function. The submission elsewhere claimed that the main objective of CF treatment is to minimise the rate of deterioration (in the lung, as measured by ppFEV<sub>1</sub>, and elsewhere) over time.

- 6.18 The submission described tezacaftor/ivacaftor as non-inferior in terms of pulmonary exacerbations and BMI outcomes. The PBAC has previously acknowledged that “a reduction in pulmonary exacerbations is an important clinical outcome for CF patients” (lumacaftor/ivacaftor (12+ year olds), PSD July 2018).
- 6.19 The ESC considered that the claim of non-inferior effectiveness, compared with lumacaftor/ivacaftor, was reasonable in the short-term based on the information in the submission. However, the ESC noted that that only 24 weeks of extension data from Study 110 were available, compared with 96 weeks from PROGRESS for lumacaftor/ivacaftor (see Figure 2).

Figure 2: Absolute change in ppFEV1 across trials, (EVOLVE, Study 110, TRAFFIC and TRANSPORT POOLED, PROGRESS)



Abbreviations: Ext=extension, ppFEV1= percent predicted forced expiratory volume in one second

Note: CI for the ppFEV<sub>1</sub> in the interim analysis of Study 110 were not reported (TGA CER)

Source: Compiled by the Commentary based on Table 2.1.28, p107 of the submission; Table 11-4, p131 of CSR TRAFFIC; Table 11-5, p141 of CSR TRANSPORT; Table 11-2 p102 of CSR PROGRESS, Table 7.3.7, p124 TGA CER

- 6.20 The submission described tezacaftor/ivacaftor as non-inferior to lumacaftor/ivacaftor for overall AE outcomes. The ESC considered this was reasonable.
- 6.21 The PBAC considered that the claim of non-inferior effectiveness and safety were adequately supported by the evidence presented. However, the PBAC noted the long-term effectiveness of tezacaftor/ivacaftor for this lifelong treatment and disease was associated with even greater uncertainty than lumacaftor/ivacaftor with only 24 weeks of extension data from Study 110 available (compared with 96 weeks from PROGRESS for lumacaftor/ivacaftor).

### Economic analysis

- 6.22 The submission stated that it did not present an economic evaluation as the sponsor was not seeking a price premium for tezacaftor/ivacaftor and there are no other

differences in administration (or other costs) that distinguish the two therapies. The evaluation and the ESC considered this was not appropriate; in the absence of a superiority claim, a cost-minimisation analysis should have been presented.

- 6.23 The PSCR presented a cost-minimisation comparison which assumed no difference in adverse events and the following equi-effective doses: tezacaftor 100 mg once daily and ivacaftor 150 mg every 12 hours (q12h) is equi-effective to lumacaftor 400 mg q12h /ivacaftor 250 mg q12h. The ESC considered this would only be reasonable if the two regimens have equivalent dose exposure; it is possible that there are fewer dose reductions required with tezacaftor/ivacaftor potentially resulting in a different dose exposure to achieve comparable treatment effects. The PBAC noted that while there were fewer treatment-related AEs in the EVOLVE trial compared with the TRAFFIC and TRANSPORT trials, there were no significant differences between AEs leading to discontinuations (Table 6). The PBAC considered that based on the overall available evidence, it would be reasonable to assume that the dose exposures of tezacaftor/ivacaftor and lumacaftor/ivacaftor were not dissimilar.
- 6.24 Despite the claim of non-inferiority and that a price premium was not being sought, the ESC noted that the submission proposed a higher DPMQ for tezacaftor/ivacaftor (\$21,000) compared with that for lumacaftor/ivacaftor (\$18,750, public hospital). The submission did not provide justification as to why the proposed price was higher. The PSCR stated that “the DPMQ for tezacaftor/ivacaftor is higher than that for lumacaftor/ivacaftor because tezacaftor/ivacaftor represents an important further development in treating the underlying cause of CF. It is the only disease-modifying treatment approved in most international markets for patients aged  $\geq 12$  years who have an RF mutation, as well as providing another treatment option for the F508del homozygous patients who are not currently helped by lumacaftor/ivacaftor. However, we reiterate that the effective price being offered is the same as lumacaftor/ivacaftor.”

### ***Drug cost/patient/year***

- 6.25 The proposed published price in the submission was \$21,000 per 28-day pack, which equates to an annual cost per patient of \$273,938 ( $\$21,000/28 \text{ day pack} \times 365.25 \text{ days per year}$ ). The submission proposed an intended annual effective price of \$[REDACTED] per patient for tezacaftor/ivacaftor to be implemented through subsidisation caps through a Risk Sharing Arrangement. The published DPMQ (public hospital) for lumacaftor/ivacaftor is \$18,750 per 28 day-pack, which equates to an annual cost per patient of \$244,587 ( $\$18,750/28 \text{ day pack} \times 365.25 \text{ days per year}$ ).

### ***Estimated PBS usage & financial implications***

- 6.26 This submission was not considered by DUSC. The submission did not provide any estimates of the anticipated impact on the PBS associated with the listing of tezacaftor/ivacaftor. The evaluation considered this was not appropriate.

- 6.27 The submission assumed that, given the cost-equivalence of tezacaftor/ivacaftor with lumacaftor/ivacaftor, there would be no financial impact to the PBS of listing tezacaftor/ivacaftor for CF patients aged 12 years and older who are homozygous for the F508del-CFTR mutation.
- 6.28 The submission assumed the number of prescriptions would not increase, as tezacaftor/ivacaftor prescriptions would replace the expected lumacaftor/ivacaftor prescriptions. As such, the submission assumed no financial impact to the MBS from the listing of tezacaftor/ivacaftor as the administration and monitoring requirements of tezacaftor/ivacaftor were expected to be the same as lumacaftor/ivacaftor. The evaluation considered this may be reasonable, with the exception that the lower drug-drug interactions (DDI) associated with tezacaftor/ivacaftor may result in uptake among patients who would otherwise not have received lumacaftor/ivacaftor due to interactions with hormonal-contraceptives.
- 6.29 The PSCR claimed that “the extent of switching from lumacaftor/ivacaftor is expected to be modest, with an Australian clinical advisory board indicating they would only switch patients when clinically indicated (e.g., patient wishes to use hormonal contraception, patient experiences AEs on lumacaftor/ivacaftor, patient is not responding to lumacaftor/ivacaftor or DDI concerns), but otherwise patients would remain on lumacaftor/ivacaftor”. The ESC disagreed and considered that the uptake of tezacaftor/ivacaftor is likely to be high, particularly among patients wishing to use hormonal contraceptives and given that tezacaftor/ivacaftor is associated with a lower rate of treatment-related AEs, less DDI concerns and a perception that it may be a more effective treatment in terms of lung function improvement, compared with lumacaftor/ivacaftor.
- 6.30 The PSCR further claimed that “There will be no impact to the PBS budget as prescribing expenditure for both lumacaftor/ivacaftor and tezacaftor/ivacaftor will be limited by the existing financial cap...the Sponsor can confirm that even though only listed in October 2018, Orkambi® use [REDACTED] the cap, and therefore it is [REDACTED] that the cap [REDACTED] if both products were to be listed. Therefore, the claim of [REDACTED].” The ESC agreed that if the subsidisation caps [REDACTED] through lumacaftor/ivacaftor [REDACTED] within the existing Deed of Agreement would result in [REDACTED]. Nevertheless, the ESC considered the submission should have presented utilisation and financial estimates, including the impact with and without the subsidisation caps through the current Deed of Agreement for lumacaftor/ivacaftor, and the share of the market likely to be taken by tezacaftor/ivacaftor, in line with the PBAC Guidelines. Moreover, the ESC noted that exceeding the subsidisation cap would not be sufficient to achieve the intended annual cost of \$ [REDACTED] per patient; rather, the estimated utilisation that was used to set the subsidisation cap for each year would need to be met or exceeded (see *Financial Management – Risk Sharing Arrangements* for further details).

### **Quality Use of Medicines**

- 6.31 The submission did not present any information regarding quality use of medicines. However, some potential for medication errors exists given the differences in daily dosage administration (1 tablet containing tezacaftor/ivacaftor to be administered in the morning and 1 tablet containing ivacaftor only approximately 12 hours later). This potential issue was addressed in the risk management plan (RMP) where the following was stated: “The 2 tablets are visually distinguishable (tablet size, colour, printing/debossing) and clearly marked in the label. Furthermore, patients with CF and/or their caregivers are accustomed with the administration of drugs and coordination of multiple therapies in their standard of care. This familiarity may further reduce the likelihood of medication errors.”
- 6.32 The ESC considered that an additional quality use of medicines issue is the adjustment required when patient are co-prescribed a moderate or strong CYP3A inhibitor.

### **Financial Management – Risk Sharing Arrangements**

- 6.33 The submission stated that the use of tezacaftor/ivacaftor in this indication should be captured within the scope of the current lumacaftor/ivacaftor Deed of Agreement. As such, the submission proposed that the listing for tezacaftor/ivacaftor be included under the same financial cap arrangements, including an intended annual price of \$ [REDACTED] per patient, and the same MAP requirements that apply currently to lumacaftor/ivacaftor.

#### Estimated Government expenditure per patient for year 1 for lumacaftor/ivacaftor

- 6.34 The ESC noted that the use of subsidisation caps through the current Deed of Agreement to achieve the intended annual price of \$ [REDACTED] per patient is associated with a significant risk that the Government would pay a higher amount. This is because realisation of this price is achieved via subsidisation caps and therefore dependent on estimated utilisation being achieved. In this regard, the ESC requested that the Department provide the PBAC with an update on utilisation of lumacaftor/ivacaftor since listing on the PBS on 1 October 2018 and an assessment of the likelihood of achieving the price of \$ [REDACTED] per patient in Year 1 of listing.
- 6.35 The Department advised the PBAC that the subsidisation cap for Year 1 of listing was set based on 10,000 – 50,000 prescriptions (or less than 10,000 full-time equivalent (FTE) patients receiving less than 10,000 prescriptions per year) being dispensed in

Year 1 (see Table 7). Table 8 presents the number of prescriptions and government expenditure for lumacaftor/ivacaftor for the first four months of listing.

**Table 7: Subsidisation caps for lumacaftor/ivacaftor by year of listing**

Year of listing	FTE patients	Prescriptions*	Subsidisation cap (\$/patient)	Minimum subsidisation cap if MAP conditions not met (\$22k/patient after the first 2.5 years of listing)
Year 1	█	█	█	█
Year 2	█	█	█	█
Year 3	█	█	█	█
Year 4	█	█	█	█
Year 5	█	█	█	█

FTE = full-time equivalent, MAP = Managed Access Program.

\*Assuming 11 prescriptions per FTE patient per year.

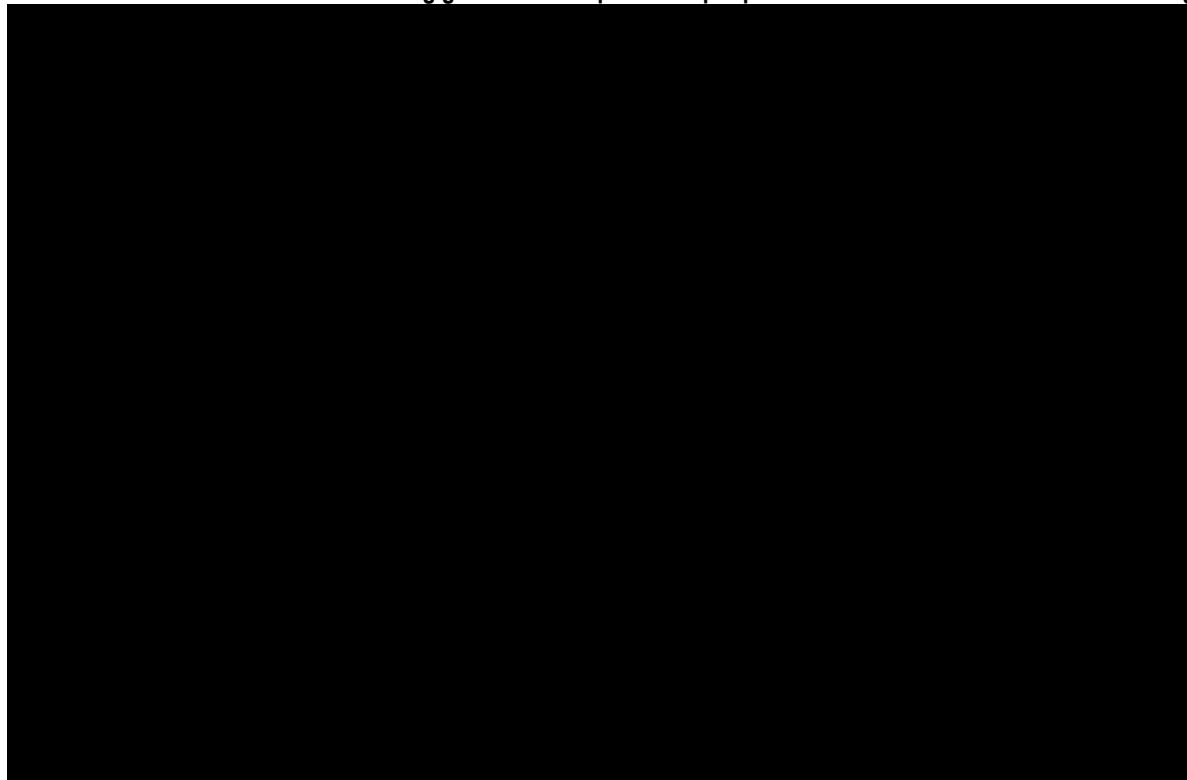
**Table 8: Utilisation of lumacaftor/ivacaftor (by month of processing), October 2018 to January 2019**

	Oct 2018	Nov 2018	Dec 2018	Jan 2019	Total
<b>Prescriptions</b>	█	█	█	█	█
<b>Government Expenditure</b>	█	█	█	█	█

Data extracted on 4 February 2019 based on month of processing.

6.36 Figure 3 illustrates four scenarios for utilisation for the remainder of Year 1 of listing and the resulting government expenditure per patient (see legend). For the most optimistic scenario, which treated less than 10,000 patients in February 2019 and for the remainder of Year 1, Government expenditure per patient would be around \$█ – higher than the intended annual price of \$█ per patient.

Figure 3: Lumacaftor/ivacaftor prescriptions based on month of processing (October 2018-January 2019) with four scenarios for utilisation and the resulting government expenditure per patient for the remainder of Year 1 of listing



Data extracted on 4 February 2019.

- 6.37 The pre-PBAC response stated that the utilisation data may be misleading given it is based only on the first four months of listing. The pre-PBAC response stated that very little uptake would be possible in the first month of listing (October 2018) and that uptake may have been lower in the December/January holiday period; the sponsor expects around less than 10,000 patients will initiate treatment in the first year of listing.
- 6.38 The PBAC noted the update on utilisation of lumacaftor/ivacaftor since its listing on 1 October 2018 provided by the Department. While the PBAC acknowledged that it was relatively early to look at utilisation of lumacaftor/ivacaftor, it considered that there was enough information available to judge that Government expenditure per patient will be significantly more than \$ [REDACTED] in Year 1 of listing. The PBAC considered that utilisation for Year 1 was more likely to fall between scenarios B and C, resulting in expenditure of between \$ [REDACTED] and \$ [REDACTED] per patient for Year 1. Accordingly, the PBAC considered that Government expenditure on lumacaftor/ivacaftor per patient in Year 1 is likely to be significantly higher than what was considered to be acceptably cost effective by the PBAC in July 2018 (paragraph 7.3, July 2018 PSD).
- 6.39 The PBAC considered that the lower than expected uptake of lumacaftor/ivacaftor could be explained in part by the significant hospital resources required to initiate

patients on treatment as described by the clinician during the sponsor hearing (see paragraph 6.3). The PBAC noted that it was previously unaware that treatment initiation may be associated with admission to hospital and that the costs of these significant hospital resources had not been taken into account in estimating the cost effectiveness of lumacaftor/ivacaftor.

#### Managed Access Program (MAP)

- 6.40 The submission did not provide details as to how tezacaftor/ivacaftor would be included in the existing MAP without limiting the availability of longer-term data for lumacaftor/ivacaftor. The PSCR argued that tezacaftor/ivacaftor patients should not be included “in the actual MAP data collection process *per se* given that i) the earliest possible listing date for tezacaftor/ivacaftor is one year into the MAP follow-up period, ii) only a small number of patients are expected to switch to tezacaftor/ivacaftor treatment, iii) the reasons for switching will be varied and include avoidance of DDIs and use of hormonal contraception, iv) there could potentially be periods of interruption between treatments, v) any incident (treatment-naïve) patients commencing tezacaftor/ivacaftor will have insufficient follow-up data and vi) new therapies will potentially become available to further complicate the situation in early 2021”. Subsequent to the PSCR, the sponsor confirmed to the Department that it does not intend to run a MAP for tezacaftor/ivacaftor. The sponsor proposed instead that any impact of the rate of decline in ppFEV<sub>1</sub> for patients treated with lumacaftor/ivacaftor on the Year 3-5 subsidisation caps in the lumacaftor/ivacaftor deed be applied to both the existing and requested listings of lumacaftor/ivacaftor and tezacaftor/ivacaftor and regardless of which CFTR gene mutation the patient has (RF or homozygous for F508del).
- 6.41 In its July 2018 recommendation for lumacaftor/ivacaftor (paragraph 6.78), the PBAC “noted that the sponsor plans to bring forward new treatments for patients who are homozygous for the F508del mutation in the CFTR gene, with tezacaftor with ivacaftor currently undergoing regulatory review and a triple therapy combination treatment in clinical trials. The PBAC recognised that this might limit the availability of longer term data for lumacaftor with ivacaftor but considered that the MAP could allow the PBAC to be provided with longer term data for patients treated continuously with lumacaftor with ivacaftor, as well as treatment with tezacaftor with ivacaftor or triple therapy, or through consecutive periods of treatment with more than one of these regimens” (paragraph 6.78, lumacaftor/ivacaftor, PSD July 2017). Accordingly, the ESC considered that it would be appropriate to include consecutive periods of treatment with one or more of lumacaftor/ivacaftor, tezacaftor/ivacaftor and other future available CFTR modulators (such as triple therapy) in the current lumacaftor/ivacaftor MAP, in line with the PBAC’s stated intention in July 2018. The ESC considered that the arguments in the PSCR were not impediments to including patients who switch treatment from lumacaftor/ivacaftor to tezacaftor/ivacaftor in the MAP. Furthermore, the ESC considered that if patients switching from lumacaftor/ivacaftor to tezacaftor/ivacaftor were excluded, this may undermine the effectiveness of the

MAP to ensure that the price paid for lumacaftor/ivacaftor and, by extension, for tezacaftor/ivacaftor is consistent with the evidence.

- 6.42 The PBAC advised that the same terms of the MAP that currently apply to lumacaftor/ivacaftor (including any reduction in the price per patient resulting from the MAP) should also apply to tezacaftor/ivacaftor. The PBAC further advised that tezacaftor/ivacaftor should be listed for patients who are homozygous for the F508del mutation with nil financial impact to Government. The PBAC agreed with the ESC that excluding patients treated with tezacaftor/ivacaftor from data collection under the MAP would compromise the effectiveness of the MAP, especially if switching to tezacaftor/ivacaftor is more likely to occur in patients with a poor response to treatment with lumacaftor/ivacaftor. In this regard, the PBAC considered that treatment with one or more of lumacaftor/ivacaftor and tezacaftor/ivacaftor should be treated as consecutive periods of treatment for the purposes of the data collection required through the MAP (i.e., patients crossing over to treatment with tezacaftor/ivacaftor should be treated as if they received continuous treatment with lumacaftor/ivacaftor).

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the Authority Required listing of tezacaftor with ivacaftor, on the basis that it should be available only under special arrangements under Section 100 (Highly Specialised Drugs Program) for the treatment of patients with CF aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene. The PBAC made its recommendation for tezacaftor/ivacaftor for this patient population on a cost-minimisation basis to lumacaftor/ivacaftor. The PBAC advised that the same Managed Access Program (MAP) requirements that currently apply to lumacaftor/ivacaftor should also apply to tezacaftor/ivacaftor. The PBAC recommended the special arrangements and circumstances described in the tables in section 8.
- 7.2 The PBAC recognised the potential clinical value of an additional CFTR modulator in the treatment of patients with CF aged 12 years or older who are homozygous for the F508del mutation. The PBAC acknowledged the potential benefit of tezacaftor/ivacaftor for patients who require medications contraindicated for concomitant use with lumacaftor/ivacaftor. The PBAC noted the many consumer comments and correspondence from Cystic Fibrosis Australia in support for subsidised access to tezacaftor/ivacaftor.
- 7.3 The PBAC accepted that lumacaftor/ivacaftor was the appropriate main comparator for the requested population.
- 7.4 The PBAC noted the indirect treatment comparison comparing outcomes from the tezacaftor/ivacaftor EVOLVE trial with the pooled results from the lumacaftor/ivacaftor TRAFFIC and TRANSPORT trials. The PBAC considered the results

of the indirect treatment comparison supported a claim that tezacaftor/ivacaftor is non-inferior in terms of comparative effectiveness and safety to lumacaftor/ivacaftor in the short-term. The PBAC noted the absolute change in ppFEV<sub>1</sub> achieved with tezacaftor/ivacaftor compared with baseline was 1.59% (95% CI: 0.17, 3.01; p=0.028) greater than that observed with lumacaftor/ivacaftor at 24 weeks; however, the PBAC considered the clinical significance of this difference to be uncertain. The PBAC noted there was no significant difference in the number of pulmonary exacerbations or hospitalisations or in absolute change in BMI between patients treated with tezacaftor/ivacaftor and lumacaftor/ivacaftor.

- 7.5 The PBAC noted that while the interim results from the extension, Study 110 supported the maintenance of a treatment effect (in terms of the absolute change in lung function in ppFEV<sub>1</sub> from baseline) beyond 24 weeks (up to 48 weeks of continuous treatment, including 24 weeks in EVOLVE), it was unknown whether the treatment effect would be maintained longer term or whether the treatment effect would translate to a gain in life expectancy. The PBAC noted the long-term effectiveness of treatment with tezacaftor/ivacaftor for this lifelong disease was associated with even greater uncertainty than lumacaftor/ivacaftor, with only 24 weeks of extension data from Study 110 available (compared with 96 weeks of extension data from PROGRESS for lumacaftor/ivacaftor).
- 7.6 Overall, the PBAC considered that the claim of non-inferior effectiveness and safety compared with lumacaftor/ivacaftor was adequately supported by the evidence presented.
- 7.7 The PBAC considered the equi-effective doses were tezacaftor 100 mg once daily/ivacaftor 150 mg q12h and lumacaftor 400 mg q12h/ivacaftor 250 mg q12h.
- 7.8 The PBAC recalled that in July 2018 it recommended lumacaftor/ivacaftor on the basis that the cost-effectiveness of listing would be acceptable if the following measures were implemented to contain risks associated with the cost-effectiveness and overall cost of the drug to the PBS:
- A MAP to allow patients to access treatment whilst providing the sponsor with an extended period to provide further data to satisfy the PBAC that the differences in the rates of decline in lung function (ppFEV<sub>1</sub>) and pulmonary exacerbations observed over the 96 week trial period are sustained over a longer time period of at least 4 years in real clinical practice. If, by the end of the two and a half year initial period of the MAP, the sponsor's assumptions on rate of decline have not been substantiated or have only been partially substantiated, through a submission to the PBAC and the PBAC affirming the cost-effectiveness of the medicine, the PBAC considered that the price paid for lumacaftor with ivacaftor should reduce to a level consistent with the evidence provided.
  - A Special Pricing Arrangement to give effect to a price of \$ [REDACTED] per patient per year; and

- Caps on total expenditure in line with estimated utilisation.
- 7.9 The PBAC noted the effectiveness of tezacaftor/ivacaftor was even more uncertain than that for lumacaftor/ivacaftor given the available data were less mature than the data available for lumacaftor/ivacaftor. On this basis, the PBAC advised that the same MAP requirements that currently apply to lumacaftor/ivacaftor (including any reduction in the price per patient resulting from the MAP) should also apply to tezacaftor/ivacaftor to manage risks around the uncertain effectiveness and whether the treatment benefit in terms of the decrease in rate of decline in lung function would be sustained in the longer term. The PBAC considered that excluding patients treated with tezacaftor/ivacaftor from data collection under the MAP would compromise the effectiveness of the MAP, especially if switching to tezacaftor/ivacaftor is more likely to occur in patients with a poor response to treatment with lumacaftor/ivacaftor. In this regard, the PBAC considered that treatment with one or more of lumacaftor/ivacaftor and tezacaftor/ivacaftor should be treated as consecutive periods of treatment for the purposes of the data collection required through the MAP (i.e., patients crossing over to treatment with tezacaftor/ivacaftor should be treated as if they received continuous treatment with lumacaftor/ivacaftor).
- 7.10 The PBAC noted the advice from the Department regarding current utilisation of lumacaftor/ivacaftor and that Government expenditure per patient in Year 1 of listing is likely to be significantly higher than what was considered acceptably cost effective (i.e. \$ [REDACTED] per patient per year) in its July 2018 recommendation (see paragraph 6.39). The PBAC advised that it would be appropriate for the Department to pursue alternative arrangements through which the price of \$ [REDACTED] per patient for tezacaftor/ivacaftor and lumacaftor/ivacaftor could be achieved, for example, such as through reducing the subsidisation caps in the current Deed of Agreement, or by implementing a Special Pricing Arrangement, as previously suggested in the July 2018 recommendation.
- 7.11 Overall, the PBAC further advised that, consistent with the evidence presented and the claim of non-inferior comparative effectiveness and safety, the price paid for tezacaftor/ivacaftor should be no higher than the price of \$ [REDACTED] per patient per year (pending the outcome of the MAP), and considered tezacaftor/ivacaftor should be listed with no additional cost to Government.
- 7.12 The PBAC considered that the requested higher DPMQ for tezacaftor/ivacaftor (\$21,000), compared with lumacaftor/ivacaftor (\$18,750), was not justified by the submission given the request for listing tezacaftor/ivacaftor on a cost-minimisation basis to lumacaftor/ivacaftor. The PBAC further considered a higher DPMQ had the potential to misinform patients and prescribers as to the PBAC's considerations of the relative benefits of the two therapies (given the PBAC principle of paying more for better outcomes).

- 7.13 The PBAC considered that the restriction should not allow patients to be treated with lumacaftor/ivacaftor and tezacaftor/ivacaftor concurrently and that flow-on changes would be required to the existing lumacaftor/ivacaftor restriction.
- 7.14 The PBAC considered it would be appropriate to include prescribing instructions in the tezacaftor/ivacaftor restriction specifying the dose adjustments required if the patient is concomitantly receiving a moderate or strong CYP3A inhibitor (see paragraph 2.4). The PBAC also considered it would be appropriate for the restriction to state that tezacaftor/ivacaftor is not PBS-subsidised in patients receiving CYP3A4 inducers, in line with the TGA approved Product Information and the current restriction for ivacaftor.
- 7.15 The PBAC considered that tezacaftor/ivacaftor should be treated as interchangeable with lumacaftor/ivacaftor, though noting that there may be discrete patient populations that respond to one of those combinations, but not the other.
- 7.16 The PBAC advised that tezacaftor/ivacaftor is not suitable for prescribing by nurse practitioners.
- 7.17 The PBAC recommended that the Early Supply Rule should apply.
- 7.18 The PBAC noted the submission is not eligible for an Independent Review, because the PBAC has made a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

### 8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer		
TEZACAFTOR + IVACAFTOR (&) IVACAFTOR Tezacaftor 100 mg + ivacaftor 150 mg tablet [28] (&) 1 ivacaftor 150 mg tablet [28], 1 pack	1	5	Symdeko®	Vertex (Australia) Pty Ltd	Pharmaceuticals

<b>Category / Program</b>	Section 100 – Highly Specialised Drugs Program
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>PBS Indication:</b>	Cystic Fibrosis
<b>Treatment phase:</b>	Initial treatment
<b>Restriction:</b>	<input type="checkbox"/> Restricted benefit <input checked="" 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 type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	Must be treated by a specialist respiratory physician with expertise in cystic fibrosis, OR

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	<p>Must be treated in consultation with a specialist respiratory physician with expertise in cystic fibrosis if attendance is not possible due to geographic isolation; AND The treatment must be the sole PBS-subsidised cystic fibrosis transmembrane conductance regulator (CFTR) modulator for this condition; AND Must be treated in a centre with expertise in cystic fibrosis, OR Must be treated in consultation with a centre with expertise in cystic fibrosis if attendance is not possible due to geographic isolation.</p>
<b>Clinical criteria:</b>	<p>Patient must be homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene; AND The treatment must be given concomitantly with standard therapy for this condition.</p>
<b>Population criteria:</b>	<p>Patient must be 12 years of age or older.</p>
<b>Prescriber Instructions:</b>	<p>The patient must be registered in the Australian Cystic Fibrosis Database Registry.</p> <p>Treatment must not be given to a patient who has an acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease in the last 4 weeks prior to commencing this drug.</p> <p>For the purposes of this restriction, PBS subsidised 'CFTR modulator' means ivacaftor, lumacaftor/ivacaftor and tezacaftor/ivacaftor.</p> <p>Dosage of tezacaftor with ivacaftor is tezacaftor 100 mg/ivacaftor 150 mg and ivacaftor 150 mg tablets on alternate days if the patient is concomitantly receiving one of the following moderate CYP3A4 drugs inhibitors: amprenavir, aprepitant, atazanavir, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil.</p> <p>Dosage of tezacaftor with ivacaftor is tezacaftor 100 mg/ivacaftor 150 mg twice weekly (approximately 3 to 4 days apart) if the patient is concomitantly receiving one of the following strong CYP3A4 inhibitors: boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole.</p> <p>Tezacaftor with ivacaftor is not PBS-subsidised for this condition in a patient who is currently receiving one of the following CYP3A4 inducers:</p> <p>Strong CYP3A4 inducers: avasimibe, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's wort</p> <p>Moderate CYP3A4 inducers: bosentan, efavirenz, etravirine, modafinil, nafcilin</p> <p>Weak CYP3A4 inducers: armodafinil, echinacea, pioglitazone, rufinamide.</p> <p>The authority application must be in writing and must include: (1) a completed authority prescription form; and (2) a completed Cystic Fibrosis Tezacaftor with Ivacaftor Authority Application Supporting Information Form; and and (3) a copy of the pathology report detailing the molecular testing for the patient being homozygous for the F508del mutation on the CFTR gene; and (4) the result of a FEV<sub>1</sub> measurement performed within a month prior to the date of application. Note: FEV<sub>1</sub>, must be measured in an accredited pulmonary function laboratory, with documented no acute infective exacerbation at the time FEV<sub>1</sub> is measured; and</p>

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	<p>(5) evidence that the patient has either chronic sinopulmonary disease or gastrointestinal and nutritional abnormalities; and</p> <p>(6) a copy of a current medication history, including any CYP3A4 inhibitors or CYP3A4 inducers; and</p> <p>(7) height and weight measurements at the time of application; and</p> <p>(8) a baseline measurement of the number of days of CF-related hospitalisation (including hospital-in-the home) in the previous 12 months.</p>
<p><b>Administrative Advice:</b></p>	<p><b>Managed Access Program:</b></p> <p>This medicine has been listed on the PBS via a Managed Access Program (MAP). The Pharmaceutical Benefits Advisory Committee (PBAC) made its recommendation on the basis of 48 weeks of data for this medicine and 96 weeks of data for lumacaftor with ivacaftor in children aged 12 years and over. Information about the long term benefits of this medicine and lumacaftor with ivacaftor will be collected and analysed under this MAP. For more information on Managed Access Programs, please visit <a href="http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/2015-03/march-2015-other-matters-managed-access-programme-framework">http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/2015-03/march-2015-other-matters-managed-access-programme-framework</a>.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a></p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>No increase in the maximum quantity or number of units may be authorised.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a></p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>

<p><b>Category / Program</b></p>	<p>Section 100 – Highly Specialised Drugs Program</p>
<p><b>Prescriber type:</b></p>	<p><input type="checkbox"/>Dental <input checked="" type="checkbox"/>Medical Practitioners <input type="checkbox"/>Nurse practitioners <input type="checkbox"/>Optometrists <input type="checkbox"/>Midwives</p>
<p><b>PBS Indication:</b></p>	<p>Cystic Fibrosis</p>
<p><b>Treatment phase:</b></p>	<p>Continuing treatment</p>

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<b>Restriction:</b>	<input type="checkbox"/> Restricted benefit <input checked="" 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 type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	<p>Must be treated by a specialist respiratory physician with expertise in cystic fibrosis, OR          Must be treated in consultation with a specialist respiratory physician with expertise in cystic fibrosis if attendance is not possible due to geographic isolation;          AND          The treatment must be the sole PBS subsidised cystic fibrosis transmembrane conductance regulator (CFTR) modulator for this condition;          AND          Must be treated in a centre with expertise in cystic fibrosis, OR          Must be treated in consultation with a centre with expertise in cystic fibrosis if attendance is not possible due to geographic isolation.</p>
<b>Clinical criteria:</b>	<p>Patient must have previously received PBS-subsidised treatment with this drug for this condition          AND          The treatment must be given concomitantly with standard therapy for this condition.</p>
<b>Population criteria</b>	<p>Patient must be 12 years of age or older.</p>
<b>Prescriber Instructions</b>	<p>Treatment must not be given to a patient who has an acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease in the last 4 weeks prior to commencing this drug.</p> <p>Patients who have an acute infective exacerbation at the time of assessment for continuing therapy may receive an additional one month's supply in order to enable the assessment to be repeated following resolution of the exacerbation.</p> <p>For the purposes of this restriction, PBS subsidised 'CFTR modulator' means ivacaftor, lumacaftor/ivacaftor and tezacaftor/ivacaftor.</p> <p>Dosage of tezacaftor with ivacaftor is tezacaftor 100 mg/ivacaftor 150 mg and ivacaftor 150 mg tablets on alternate days if the patient is concomitantly receiving one of the following moderate CYP3A4 drugs inhibitors: amprenavir, aprepitant, atazanavir, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil.</p> <p>Dosage of tezacaftor with ivacaftor is tezacaftor 100 mg/ivacaftor 150 mg twice weekly (approximately 3 to 4 days apart) if the patient is concomitantly receiving one of the following strong CYP3A4 inhibitors: boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole</p> <p>Tezacaftor with ivacaftor is not PBS-subsidised for this condition in a patient who is currently receiving one of the following CYP3A4 inducers:</p> <p>Strong CYP3A4 inducers: avasimibe, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's wort</p> <p>Moderate CYP3A4 inducers: bosentan, efavirenz, etravirine, modafinil, nafcillin</p> <p>Weak CYP3A4 inducers: armodafinil, echinacea, pioglitazone, rufinamide.</p> <p>The authority application must be in writing and must include:          (1) a completed authority prescription form; and</p>

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	<p>(2) a completed Cystic Fibrosis Tezacaftor with Ivacaftor Authority Continuing Application Supporting Information Form; and</p> <p>(3) the result of a FEV1 measurement performed within a month prior to the date of application. Note: FEV1, must be measured in an accredited pulmonary function laboratory, with documented no acute infective exacerbation at the time FEV1 is measured; and</p> <p>(4) a copy of a current medication history, including any CYP3A4 inhibitors or CYP3A4 inducers; and</p> <p>(5) height and weight measurements at the time of application; and</p> <p>(6) the number of days of CF-related hospitalisation (including hospital-in-the home) in the previous 6 months.</p>
<p><b>Administrative Advice:</b></p>	<p><b>Managed Access Program:</b></p> <p>This medicine has been listed on the PBS via a Managed Access Program (MAP). The Pharmaceutical Benefits Advisory Committee (PBAC) made its recommendation on the basis of 96 weeks of data for 48 weeks of data for this medicine and lumacaftor with ivacaftor in children aged 12 years and over. Information about the long term benefits of this medicine and lumacaftor with ivacaftor will be collected and analysed under this MAP. For more information on Managed Access Programs, please visit <a href="http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/2015-03/march-2015-other-matters-managed-access-programme-framework">http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/2015-03/march-2015-other-matters-managed-access-programme-framework</a>.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a></p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>No increase in the maximum quantity or number of units may be authorised.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a></p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>

- 8.2 Make the following flow on change to lumacaftor/ivacaftor (lumacaftor 200 mg + ivacaftor 125 mg tablet, 112; PBS item numbers 11463H and 11466L): Add additional clinical criterion, 'The treatment must be the PBS subsidised sole cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy for this condition',

and additional prescriber instructions, 'For the purposes of this restriction, PBS subsidised 'CFTR modulator's means ivacaftor, lumacaftor/ivacaftor and tezacaftor/ivacaftor'.

## **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**

The sponsor had no comment.