

5.08 TEZACAFTOR with IVACAFTOR, Pack containing tezacaftor 100 mg with ivacaftor 150 mg tablets and ivacaftor 150 mg tablets, Symdeko[®], 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 sets of have been presented. This PSD deals with the evidence in respect of the RF mutations listing.

1 Purpose of Application

- 1.1 The submission requested a Section 100, Authority Required listing for tezacaftor/ivacaftor for treatment of cystic fibrosis (CF) patients aged 12 years and older who have at least one residual function (RF) mutation in the CFTR gene. 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	Patients who have at least one RF mutation in the <i>CFTR</i> gene.
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	BSC for patients who have at least one RF mutation.
Outcomes	Primary outcome: <ul style="list-style-type: none"> • Absolute change from baseline in ppFEV₁. Secondary outcomes: <ul style="list-style-type: none"> • Relative change from baseline in ppFEV₁. • Pulmonary exacerbation measures. • 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). • Absolute change from baseline in CFQ-R Respiratory Domain Score. • Absolute change in sweat chloride.
Clinical Claim	Tezacaftor/ivacaftor plus BSC is superior in terms of efficacy and non-inferior in terms of safety compared to BSC alone (placebo).

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; ppFEV₁=percent predicted forced expiratory volume in one second; RF=residual function.

Source: Table 1.1.1, page 34 of the Submission.

2 Requested listing

- 2.1 The requested restriction is summarised in Table 2 and was largely consistent with the key trial, Study 108.

Table 2: Summary of the proposed restriction

Name, Restriction, Manner of administration and form	Max. Qty (packs)	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
TEZACAFTOR/IVACAFTOR (SYMDEKO®) Tezacaftor 100 mg + ivacaftor 150 mg tablet [28] (&) ivacaftor 150 mg tablet [28], 1 pack.	1	5	\$21,000	Symdeko®	Vertex

Category/Program:	Section 100 - Highly Specialised Drugs Program – Authority Required
PBS indication:	CF patients who have at least one RF mutation in the CFTR gene.
Treatment phase:	Initial
Restriction:	Patients must be 12 years or older.
Treatment criteria:	Sole PBS-subsidised disease-modifying therapy for this condition.
Clinical criteria:	RF mutation in the CFTR gene must be responsive to tezacaftor/ivacaftor and treatment must be given concomitantly with BSC.

Abbreviations: BSC= best supportive care; CF= cystic fibrosis; CFTR: Cystic fibrosis transmembrane conductance regulator; Max= maximum; PBS= Pharmaceutical Benefits Scheme; Qty= quantity; RF= residual function; Rpts= repeats.

Source: Table 1.4.2, p. 58 of the Submission.

- 2.2 The submission did not request a Special Pricing Arrangement in the form of a published versus an effective price. However, the submission proposed a reduction in the estimated gross cost of tezacaftor/ivacaftor via a subsidisation cap, to be implemented through a Risk Sharing Arrangement (RSA). 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* in section 6 for further details).
- 2.3 The proposed restriction did not fully represent the Study 108 population in that it did not include a criterion which required patients to have ppFEV₁ (percent predicted forced expiratory volume in one second) ≥40% and ≤90% of predicted normal for age, sex, and height (as per the entry criteria for Study 108). At the March 2016 PBAC meeting, the PBAC emphasised that the efficacy and safety of lumacaftor/ivacaftor in patients with ppFEV₁ <40% and >90% had not been evaluated and was unknown (lumacaftor/ivacaftor (aged 12+ years) Public Summary Document (PSD) March 2016, paragraph 2.2). Ultimately, the PBAC did not recommend the inclusion of a criterion based on ppFEV₁ for lumacaftor/ivacaftor (lumacaftor/ivacaftor (aged 12+ years) PSD July 2018, section 8).
- 2.4 The proposed listing requires presence of an RF mutation known to be responsive to tezacaftor/ivacaftor (with the list of mutations defined in Table 1 in the TGA approved Product Information) based on a positive clinical response and/or in vitro data indicating that tezacaftor/ivacaftor increases chloride transport to at least 10% over baseline. Responsiveness is determined from a panel of such known mutations (rather than de-novo testing of each patients' mutations). There is no evidence regarding the treatment effect of tezacaftor/ivacaftor if an RF mutation which does not exist in the current panel of known tezacaftor/ivacaftor responsive mutations were to be identified. The Pre-Sub-Committee Response (PSCR) indicated there is a low probability of additional mutations being identified or characterised as RF. The PSCR further noted that any new mutations would need to be in line with the TGA indication

of being proven to be responsive to treatment (see *Registration status* in section 3 for further details).

- 2.5 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.
- 2.6 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 Clinical Evaluation Report (CER) (round 2) was available. No major efficacy or safety issues were raised by the clinical evaluator. The Request for ACM's Advice, the Minutes of the ACM meeting on 6 December 2018, a TGA Delegate letter (dated 21 December 2018) requesting additional information from the Sponsor and the Sponsor's reply to that letter 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 that 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 that may result in retention of residual activity and therefore, less severe disease. RF mutations are relatively rare and lead to variable disease activity and a later onset of symptoms (page 14-15 of the submission). However, patients with RF mutations still develop significant and progressive disease with a reduced life expectancy. Compared to patients who are homozygous for the F508del mutation, studies have shown that heterozygous patients required less pancreatic enzyme substitution, had better lung function, had a lower yearly incidence of chronic *Pseudomonas aeruginosa* infection, and had better mortality rates¹. This could be interpreted as being that patients with RF mutation have less rapidly progressing disease.
- 4.3 Tezacaftor/ivacaftor is proposed as a lifelong treatment administered concomitantly with BSC in patients ≥ 12 years who have an RF mutation responsive to the treatment. The ESC noted that the evidence presented is based only on patients who are heterozygous for the F508del mutation who also have an RF mutation. It is unknown whether the Australian patient population would also consist of patients with two RF mutations in the CFTR gene.

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

5 Comparator

- 5.1 The submission nominated best supportive care (BSC) as the main comparator. The submission argued there are no treatment alternatives TGA registered available for this patient population. The ESC considered this was appropriate.

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

¹ Johansen, H. K., Nir, M., Hoiby, N., Koch, C., & Schwartz, M. (1991). Severity of cystic fibrosis in patients homozygous and heterozygous for delta F508 mutation. *Lancet* (London, England), 337(8742), 631–634.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The Sponsor requested a hearing for this item. The clinician emphasised the importance of extending treatment with tezacaftor/ivacaftor to CF patients with RF mutations. The clinician noted that patients with RF mutations may experience slower disease progression compared with those who are homozygous for the F508del mutation. However, the clinician stated that overall, patients with RF mutations have poor lung function noting that many currently require treatment to manage disease symptoms, with few patients having an FEV₁ of more than 90%, and limited life expectancy due to CF. In response to the PBAC's comment that the clinical evidence appeared to suggest that the effectiveness of ivacaftor monotherapy may be similar to that of tezacaftor/ivacaftor for this patient population, the clinician noted the short duration of the study and expressed uncertainty as to whether the study was powered to differentiate between ivacaftor and tezacaftor/ivacaftor.
- 6.2 In response to a question from the PBAC regarding why uptake of lumacaftor/ivacaftor for the F508del patient population 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 treatment failure for patients initiated with FEV₁ < 50%. The clinician claimed that most major treatment centres in Australia were following clinical protocol that 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

- 6.3 The PBAC noted and welcomed the input from individuals (137), health care professionals (2) and Organisations (2) via the Consumer Comments facility on the PBS website. The comments described the burden of CF on patients and the significant impact to their families and the potential treatment benefits of tezacaftor/ivacaftor, including for patients with an RF mutation who do not currently have access to treatment with a CFTR modulator. The comments included specific claims that treatment of cystic fibrosis patients with CFTR modulators is associated with the following benefits:
- improved quality and length of life by preventing or slowing decline in lung function
 - better pancreatic function, weight gain and growth
 - fewer pulmonary exacerbations and hospital admissions

- reduced need for physiotherapy and other medications that treat the symptoms of the disease
 - improved mental health
 - improved quality of life and fewer absences from education/work.
- 6.4 Cystic Fibrosis Australia (CFA) and Cystic Fibrosis Tasmania (CFTAS) indicated support for tezacaftor/ivacaftor to be listed on the PBS for patients who have an RF mutation. CFA and 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

- 6.5 The submission was based on one head-to-head trial, Study 108 (N=244) comparing tezacaftor/ivacaftor plus BSC with ivacaftor plus BSC and placebo plus BSC in patients aged 12 years and older who are heterozygous for the F508del-CFTR mutation and a second allele with a CFTR mutation predicted to have RF. Details of the trial presented in the submission are provided in Table 3. Ivacaftor was not a comparator for tezacaftor/ivacaftor (it is neither registered nor reimbursed in this setting); thus, results for the ivacaftor group are presented here for completeness only.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Study 108	<p>A phase 3 study to evaluate the efficacy and safety of ivacaftor and VX-661 in combination with ivacaftor in subjects aged 12 years and older with cystic fibrosis, heterozygous for the <i>F508del</i>-cystic fibrosis transmembrane conductance regulator (<i>CFTR</i>) mutation.</p> <p>A phase 3 Study to Evaluate the Efficacy and Safety of Ivacaftor and VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Heterozygous for the <i>F508del</i>-cystic Fibrosis Transmembrane Conductance Regulator (<i>CFTR</i>) Mutation.</p> <p>Rowe SM, Daines C, Ringshausen FC, <i>et al.</i> Tezacaftor–ivacaftor in RF heterozygotes with cystic fibrosis.</p> <p>Rowe SM, Davies J. <i>CFTR</i> modulation with tezacaftor/ivacaftor in patients heterozygous for <i>F508del</i> and a RF mutation.</p> <p>Rowe SM, Davies JC, Nair N, <i>et al.</i> Efficacy and safety of tezacaftor/ivacaftor and ivacaftor in patients aged ≥ 12 years with CF heterozygous for <i>F508del</i> and a RF mutation: A randomized, double-blind, placebo-controlled, crossover phase 3 study.</p> <p>Fischer R, Rowe SM, Davies JC, Nair N, Han L, Lekstrom-Himes J. Efficacy and safety of tezacaftor/ivacaftor in patients (Pts) aged ≥ 12 years with CF heterozygous for <i>F508del</i> and a RF mutation: A randomized, double-blind, placebo-controlled, crossover phase 3 study.</p>	<p>Clinical Study Report Study VX14-661-108. 12 June 2018.</p> <p>ClinicalTrials.gov identifier NCT02392234</p> <p><i>New England Journal of Medicine</i>; 2017; 337(21): 2024–2035.</p> <p><i>Pediatric Pulmonology</i>; 2017; 52(Suppl 47): 175–176.</p> <p><i>Pediatric pulmonology</i>; 2017; 52(Supplement 47): 317.</p> <p><i>Pneumologie</i>; 2018; 72(Supplement 1): S35.</p>
Study 110 (Ongoing study, insufficient data)	<p>A phase 3, open-label, rollover study to evaluate the safety and efficacy of long-term treatment with VX-661 in combination with ivacaftor in subjects aged 12 years and older with cystic fibrosis, homozygous or heterozygous for the <i>F508del</i>-<i>CFTR</i> mutation.</p> <p>A study to assess the efficacy and safety of a combination of two experimental drugs in people with cystic fibrosis (a rare hereditary lung disease).</p> <p>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</i>-<i>CFTR</i> or heterozygous for <i>F508del</i> and a RF mutation: First interim analysis results of a phase 3, open-label, rollover study.</p> <p>Flume P, Lekstrom-Himes J, Fischer Biner R, <i>et al.</i> A phase 3, open-label study of tezacaftor/ivacaftor (TEZ/IVA) therapy: Interim analysis of pooled safety, and efficacy in patients homozygous for <i>F508del</i>-<i>CFTR</i>.</p> <p>Flume P, Owen CA, Fischer Biner R, <i>et al.</i> A phase 3, open-label study of tezacaftor/ivacaftor (TEZ/IVA) therapy: Interim analysis of pooled safety, and efficacy in patients heterozygous for <i>F508del</i>-<i>CFTR</i> and a RF mutation.</p>	<p>Clinical Study Report Study VX14-661-110 13 September 2017.</p> <p>2015</p> <p><i>American journal of respiratory and critical care medicine</i>; 2018; 197(Meeting Abstracts): A7807.</p> <p><i>Journal of Cystic Fibrosis</i>. 2018; 17(Suppl 3): S64-S65.</p> <p><i>Journal of Cystic Fibrosis</i>; 2018; 17(Suppl 3): S29.</p>

Abbreviations: *CFTR*= Cystic fibrosis transmembrane conductance regulator; *IVA*= ivacaftor; *RF*= residual function; *TEZ*= tezacaftor
Source: Table 2.2.1, p.143-144 of the Submission

6.6 The key features of the direct randomised trial are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Tezacaftor/ivacaftor vs. BSC						
Study 108	244	R, DB, crossover, MC 8 weeks	Low	≥12 years, at least one RF mutation.	Primary: ppFEV ₁ Secondary: relative ppFEV ₁ , PEx, CFQ-R Respiratory Domain Score, nutritional status (BMI), sweat chloride.	Absolute change ppFEV ₁ , PEx, BMI

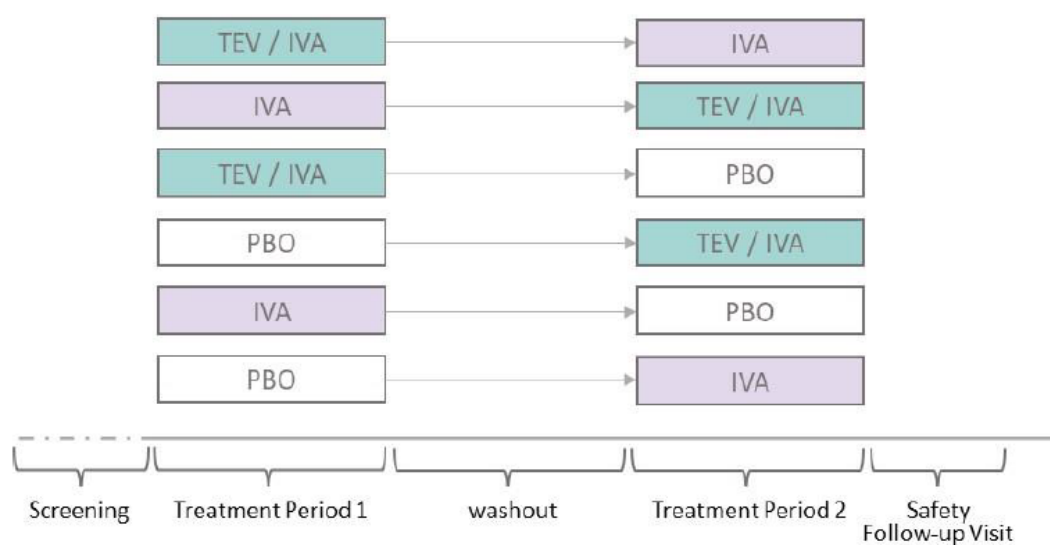
Abbreviations: BSC = best supportive care; BMI = body mass index; DB = double blind; MC = multi-centre; PEx = pulmonary exacerbation; ppFEV₁ = percent predicted forced expiratory volume in one second; R = randomised.

Source: compiled during the evaluation

6.7 The trial design had a low risk of selection, performance, detection, attrition and reporting bias. All outcomes of the trial were reported as the average of week 4 and 8 for each treatment period. Efficacy was defined in terms of intermediate outcomes (namely lung function, e.g. ppFEV₁), and the duration of follow-up was short (8 weeks in Study 108).

6.8 The ESC noted that Study 108 consisted of an 8-week treatment period followed by a washout period and an additional 8-week crossover treatment period in which patients were randomised to one of six treatment sequences, as per Figure 1. The ESC noted that Study 108 reported results from treatment periods 1 and 2 (8 weeks each). The submission did not address how the crossover design might affect the validity of the comparison of either efficacy or harm through a differential carryover effect. The PSCR provided updated data for Study 110 which reported interim results from Study 108 treatment period 2 (8 weeks, pre-treated patients) plus 16 weeks of follow-up (up to 24 weeks in total). The ESC noted that patients may have differed in terms of their baseline ppFEV₁ due to the treatment received in treatment period 1, confounding the comparison of the results from these two studies (Study 108 and Study 110).

Figure 1: Study design for Study 108



Source: Figure 2.2.1, p145 of the submission.

Abbreviations: IVA= ivacaftor; PBO= placebo; TEV= tezacaftor.

Note: The Study 108 CSR (page 63) indicated that the washout period was “at least 8 weeks”.

Comparative effectiveness

6.9 Study 108 reported statistically significant (p value < 0.0001) differences from baseline in ppFEV₁, the relative change in ppFEV₁, sweat chloride and CFQ-R Respiratory Domain Scores for tezacaftor/ivacaftor compared with BSC (Table 5).

Table 5: Linear mixed-effects model for absolute and relative change from baseline in ppFEV₁ and CFQ-R respiratory domain to the average of Week 4 and Week 8 measurements, FAS

		Placebo N=161	Ivacaftor N=156	Tezacaftor/ivacaftor N=161
Baseline ppFEV₁, mean % (SD)		62.2 (14.3)	62.1 (14.6)	62.1 (14.7)
Absolute change from baseline in ppFEV₁^a	LS mean, % (95% CI)	-0.3 (-1.2,0.6)	4.4 (3.5,5.3)	6.4 (5.6,7.3)
	LS mean treatment difference versus placebo, % (95% CI)	NA	4.7 (3.7, 5.8) p<0.0001	6.8 (5.7, 7.8) p<0.0001
Relative change from baseline in ppFEV₁^a	LS mean, % (95% CI)	-0.2 (-1.7, 1.4)	7.9 (6.4, 9.4)	11.2 (9.7, 12.7)
	LS mean difference versus placebo (95% CI)	NA	8.1 (6.3, 9.9) <0.0001	11.4 (9.6, 13.2) <0.0001
Baseline in CFQ-R respiratory domain, mean % (SD)		68.7 (18.3)	67.9 (16.9)	68.2 (17.5)
Average absolute change in CFQ-R respiratory domain^b	LS mean, % (95% CI)	-1.0 (-2.9,1.0)	8.7 (6.8,10.7)	10.1 (8.2,12.1)
	LS mean difference versus placebo (95% CI)	NA	9.7 (7.2, 12.2) <0.0001	11.1 (8.7, 13.6) <0.0001
Baseline in sweat chloride, mean mmol/L (SD)		70.2 (25.7)	72.3 (25.7)	67.0 (26.8)
Relative change from baseline in sweat chloride^c	LS mean, % (95% CI)	-0.4 (-2.3,1.5)	-4.9 (-6.7,-3.0)	-9.9 (-11.8,-8.0)
	LS mean difference versus placebo, mmol/L (95% CI)	NA	-4.5 (-6.7, -2.3) <0.0001	-9.5 (-11.7, -7.3) <0.0001

Abbreviations: CI= confidence interval; FAS= full analysis set; LS= least squares; N= number; NA=not applicable; ppFEV₁= percent predicted forced expiratory volume in one second; SE= standard error

Source: Table 2.2.14, p. 166 of the Submission, Table 2.2.17, p. 169 of the Submission, Table 2.2.18, p. 170 of the Submission.

Note: Bold text indicates a statistically significant value.

NOTE: a Sample sizes: Placebo = 160; ivacaftor = 156; tezacaftor/ivacaftor = 159

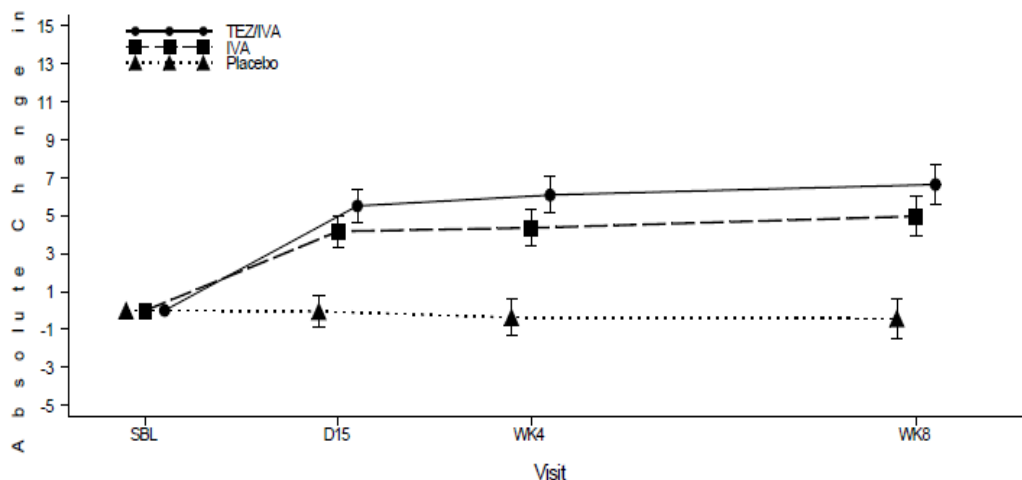
b Sample sizes: Placebo = 160; ivacaftor = 156; tezacaftor/ivacaftor = 161

c Sample sizes: Placebo = 157; ivacaftor = 155; tezacaftor/ivacaftor = 158

6.10 The results for the absolute change in ppFEV₁ showed a statistically significant difference in favour of tezacaftor/ivacaftor compared with BSC (6.8%, $p < 0.001$). The least squares (LS) mean treatment difference for ppFEV₁ was observed at the first assessment on Day 15 (5.6%) and was statistically significant ($p < 0.0001$) at all-time points from Day 15 through Week 8 (see Figure 2).

6.11 The mean CFQ-R Respiratory Domain Scores increased by more than four points in the tezacaftor/ivacaftor group (LS mean difference of 11.1 points versus placebo; 95% CI 8.7-13.6, see Table 5). The long-term maintenance of this difference is uncertain; for example, the PBAC has noted that results from the lumacaftor/ivacaftor extension study (PROGRESS) showed that at week 72 the LS mean absolute change was 5.7 points and below 4 points at week 96 (lumacaftor/ivacaftor (aged 12+ years) PSD July 2018, paragraph 6.19). A 4-point change was previously presented as the minimal clinically important difference (MCID) for the CFQ-R respiratory domain in the lumacaftor/ivacaftor (aged 12+ years) submission (PSD July 2018, paragraph 6.19).

Figure 2: MMRM analysis of absolute change from baseline in ppFEV1 at each visit, FAS

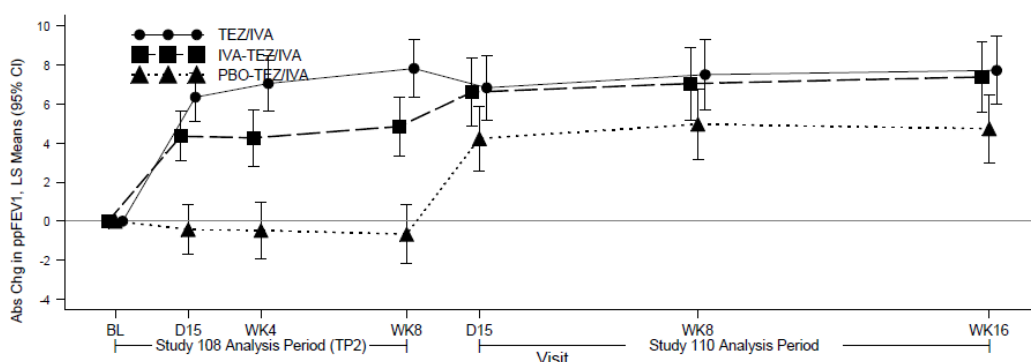


Abbreviations: SBL= study baseline; D= day; FEV= forced expiratory volume; IVA= ivacaftor; MMRM= mixed-effects model for repeated measures; TEZ= tezacaftor; WK= week

Source: Figure 2.2.2, p.167 of the Submission.

- 6.12 The point estimate of the rate of pulmonary exacerbations was lower for tezacaftor/ivacaftor than for placebo (6.8% and 11.8% respectively); however, the difference in event rates was not statistically significant (RR: 0.54; 95% CI 0.26-1.13). For lumacaftor/ivacaftor, the PBAC acknowledged that a reduction in pulmonary exacerbations was an important clinical outcome for CF patients (lumacaftor/ivacaftor (aged 12+ years) PSD July 2018, paragraph 6.17).
- 6.13 The mean absolute change from baseline in BMI was higher for tezacaftor/ivacaftor than for placebo (0.34 kg/m² and 0.18kg/m² respectively); however, given the short duration of the treatment period, the submission was unable to demonstrate that the changes in BMI and weight from baseline for tezacaftor/ivacaftor equate to improvements in nutritional status compared with placebo.
- 6.14 The PSCR presented updated data from extension Study 110 from a recent interim analysis in which 100% of enrolled patients had reached the week 16 follow-up visit (i.e. up to 24 weeks of treatment in total, including 8 weeks from treatment period 2 in Study 108) – see Figure 3.

Figure 3: MMRM analysis of absolute change from baseline in ppFEV₁ at each visit, Study 108 FAS and Study 108/110 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

- 6.15 The PSCR noted that the absolute improvements in ppFEV₁ observed in the tezacaftor/ivacaftor group during Study 108 were maintained through week 16 of Study 110. The PSCR further noted that at week 16 of Study 110, the LS mean absolute change from baseline in ppFEV₁ was 7.8% (95% CI: 6.1-9.6) in the tezacaftor/ivacaftor group. The ESC noted that as the mean ppFEV₁ at baseline for treatment period 2 had not been provided, the mean ppFEV₁ at week 16 of Study 110 was unknown.
- 6.16 Allowing for the complexity on interpreting the data from the crossover study which lasted 24 weeks (8 weeks per treatment period plus a wash-out period of at least 8 weeks) but is presented as only 8 weeks, the ESC considered that while the Study 110 interim analysis data appear to support the maintenance of treatment effect for 16 weeks beyond Study 108, the long-term efficacy of tezacaftor/ivacaftor in this patient population remains unknown.

Comparative harms

- 6.17 Allowing for the potential impact of differential carryover from the crossover design, no major differences were observed across the three study arms (see Table 6). Most subjects had adverse events (AEs) that were considered either mild or moderate in severity. Four (2.5%) patients in the tezacaftor/ivacaftor group and nine (5.6%) patients in the placebo group had Grade 3 (severe) or Grade 4 (life-threatening) AEs. There were few discontinuations due to the study drug with no discontinuations occurring in the tezacaftor/ivacaftor group and no deaths reported. Some preliminary safety results from Study 110 were available from the TGA CER for both homozygous and heterozygous to the F508del mutation patients. No major differences were identified compared to the results reported in the pivotal trial.

Table 6: Overview of AEs, Safety Set

	Placebo N=162 n (%)	Ivacaftor N=157 n (%)	Tezacaftor/ivacaftor N=162 n (%)	Risk Ratio tezacaftor/ivacaftor vs BSC (95% CI)
Number of AEs (Total)	447	342	422	
Subjects with any AEs	126 (77.8)	114 (72.6)	117 (72.2)	0.98 (0.79, 1.22)
Subjects with related AEs	38 (23.5)	31 (19.7)	37 (22.8)	1.03 (0.67, 1.59)
Subjects with AEs by strongest relationship				
Related	5 (3.1)	2 (1.3)	3 (1.9)	0.64 (0.15, 2.64)
Possibly related	33 (20.4)	29 (18.5)	34 (21.0)	1.09 (0.69, 1.73)
Unlikely related	25 (15.4)	23 (14.6)	30 (18.5)	1.27 (0.76, 2.13)
Not related	63 (38.9)	60 (38.2)	50 (30.9)	0.84 (0.59, 1.19)
Subjects with AEs by maximum severity				
Mild	63 (38.9)	55 (35.0)	58 (35.8)	0.98 (0.70, 1.36)
Moderate	54 (33.3)	51 (32.5)	55 (34.0)	1.08 (0.76, 1.53)
Severe	8 (4.9)	8 (5.1)	4 (2.5)	0.53 (0.16, 1.75)
Life-threatening	1 (0.6)	0	0	-
Subjects with Grade 3 or Grade 4 AEs	9 (5.6)	8 (5.1)	4 (2.5)	0.47 (0.15, 1.52)
Subjects with SAEs	14 (8.6)	10 (6.4)	8 (4.9)	0.61 (0.26, 1.43)
Subjects with related SAEs	2 (1.2)	2 (1.3)	0	-
Subjects with AEs leading to treatment discontinuation	1 (0.6)	2 (1.3) ^b	0	-
Subjects with AEs leading to treatment interruption	6 (3.7) ^a	5 (3.2)	2 (1.2)	0.35 (0.072, 1.74)
Subjects with AEs leading to death	0	0	0	NA

Abbreviations: AEs= adverse events; CI= confidence interval; CF= cystic fibrosis; CPK= creatine phosphokinase; MedDRA= Medical Dictionary for Regulatory activities; NA= not applicable; N/n= number; PEx= pulmonary exacerbation; SAEs= serious adverse events

^a Subject 108-015-003 had multiple life-threatening AEs (mental status changes, acute respiratory failure, pneumothorax, infective PEx of CF, and pneumonia) that were each considered serious. The study drug was interrupted, and the subject completed the study.

^b The case report form for Subject 108-301-008 incorrectly noted that the subject discontinued treatment for an SAE of blood CPK increased; however, the event occurred 1 day after the last dose of IVA in the Treatment Period, and this subject actually completed Treatment Period One. The subject did subsequently withdraw from the study during the washout period due to the event and did not participate in Period Two.

Source: Table 2.2.22, p. 174 of the Submission.

Benefits/harms

6.18 On the basis of direct evidence from Study 108 presented by the submission, the comparison of tezacaftor/ivacaftor and BSC resulted in:

- An increase in the lung capacity (as measured by ppFEV₁) of 6.8% after 8 weeks of treatment.
- No difference in the likelihood of harm.

6.19 A summary of the comparative benefits and harms for tezacaftor/ivacaftor versus BSC is presented in Table 7.

Table 7: Summary of comparative benefits and harms for tezacaftor/ivacaftor and BSC

Change from baseline in absolute change in ppFEV ₁						
	Tezacaftor/ivacaftor		BSC		Mean difference*: Tezacaftor/ivacaftor vs. BSC (95% CI)	
	N	LS Mean (95% CI)	N	LS Mean (95% CI)		
Study 108	161	6.4 (5.6, 7.3)	161	-0.3 (-1.2, 0.6)	6.8 (5.7, 7.8)	
Harms						
	Tezacaftor/ ivacaftor n/N	BSC n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				TEZ/IVA	BSC	
Patients with Grade 3 or Grade 4 AEs						
Study 108	4/162	9/162	0.47 (0.15, 1.52)	2.48	5.59	-0.03 (-0.07, 0.012)
Possibly related AE						
Study 108	34/162	33/162	1.09 (0.69, 1.73)	21.1	20.5	0.01 (-0.08, 0.10)
Patients with any AE						
Study 108	117/162	126/162	0.98 (0.79, 1.22)	72.3	78.3	-0.06 (-0.2, 0.04)

Abbreviations: AE = adverse event; BSC= best supportive care; CI = confidence interval; IVA ivacaftor; ppFEV₁ = predicted expiratory volume in one second; RD = risk difference; RR = risk ratio; SD = standard deviation; TEZ= tezacaftor

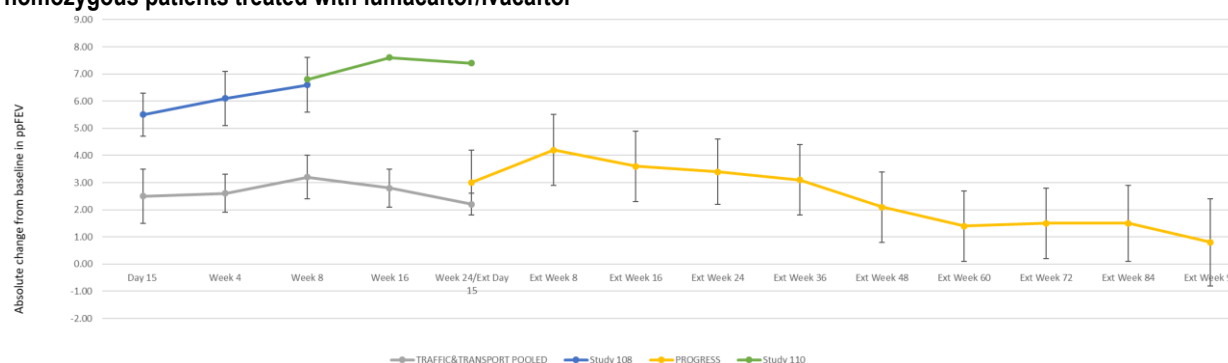
Source: Table 2.2.22, p. 174 of the Submission.

* Mean treatment duration: 7.9 weeks

Clinical claim

- 6.20 The submission claimed that tezacaftor/ivacaftor was superior in terms of effectiveness compared with BSC and non-inferior in terms of safety compared with BSC. The submission claimed that the main objective of CF treatment is to minimise the rate of deterioration (in the lung, as measured by ppFEV₁, and elsewhere) over time.
- 6.21 As per previous CFTR modulator submissions, efficacy was defined in terms of intermediate outcomes, and the duration of follow-up was short (8 weeks in Study 108), hence, the clinical claim presented in the submission was only partly supported by the evidence and the long-term implications for efficacy and safety are unknown. Data from the lumacaftor/ivacaftor PROGRESS study demonstrated that the increase in ppFEV₁ at extension week 96 (i.e. up to 120 weeks of continuous treatment) for patients homozygous for the F508del mutation was not maintained in the long-run (lumacaftor/ivacaftor (aged 12+ years) PSD July 2018, paragraph 3.6) – see Figure 4. The follow-up period for Study 108 (of 8 weeks) was shorter than that studied in patients who are homozygous for the F508del mutation (24 weeks in EVOLVE for tezacaftor/ivacaftor and TRAFFIC/TRANSPORT in lumacaftor/ivacaftor). Regarding CF treatment duration in clinical trials, the TGA CER noted that international guidelines for CF recommended that efficacy should be assessed at least with a treatment duration of at least 6 months to estimate efficacy.

Figure 4: Absolute change from baseline in ppFEV₁ at each visit for Study 108 (treatment period 2) and Study 110 in RF mutation patients treated with tezacaftor/ivacaftor, and for TRAFFIC/TRANSPORT and PROGRESS in F508del homozygous patients treated with lumacaftor/ivacaftor



Abbreviations: ppFEV₁= percent predicted forced expiratory volume in one second.
Source: prepared within the evaluation.

- 6.22 The ESC considered the claim of superior efficacy compared with BSC was supported in the short-term by the evidence from Study 108 and Study 110. However, the ESC considered the long-term comparative efficacy of tezacaftor/ivacaftor to be uncertain given the absence of data beyond 24 weeks, particularly in the context of a life-long disease.
- 6.23 The ESC noted that not all known RF mutations have clinical data to suggest a positive clinical benefit and of those RF mutations included in Study 108, each was associated with ≤ 21 patients. The ESC noted the potential heterogeneity of outcomes across patients with RF mutations and therefore considered the magnitude of effectiveness of tezacaftor/ivacaftor across the group of requested RF mutations to be uncertain. The pre-PBAC Response noted “given the rarity of these mutations, well-powered clinical studies that evaluate each individual CFTR genotype will not be possible”. The pre-PBAC Response further noted that all 10 RF mutations represented in the Australian Cystic Fibrosis Data Registry from 2015 to 2016 were included in the clinical trial.
- 6.24 The ESC noted that tezacaftor/ivacaftor was similar in terms of AEs to BSC; however, the available evidence does not inform long-term comparative safety.
- 6.25 The PBAC considered the claim of superior comparative effectiveness was reasonable in the short-term based on the available data (with 8 weeks in Study 108 and 16 weeks of extension data in Study 110); however, the PBAC noted that given the short duration of follow-up, it was unknown whether the observed improvement in ppFEV₁ would be maintained longer term in the context of a lifelong progressive disease.
- 6.26 The PBAC considered there was inadequate data to determine the comparative safety of tezacaftor/ivacaftor given the short duration of available trial data. However, the PBAC noted there were no major safety signals from the available safety data.

Economic analysis

6.27 The economic evaluations presented were a cost-utility analysis (CUA) and a cost-effectiveness analysis (CEA). Health benefits were reported as quality adjusted life years (QALYs) gained and life years gained (LYGs), respectively. The model structure was the same as that for previous CFTR modulator submissions.

6.28 The key components of the economic evaluation are presented in Table 8.

Table 8: Summary of model structure and rationale

Component	Description
Types of analysis	CUA and CEA
Outcomes	QALYs and LYGs
Time horizon	Lifetime horizon vs. 8 weeks in Study 108
Method(s) used to generate results	Individual patient microsimulation.
Health states	Changes are recorded based on individual patient underlying risk factors. Health states based on ppFEV ₁ status of normal (>90%), mild (70-90%), moderate (40-70%) and severe (<40%).
Cycle length	Four weekly cycle for the initial two years, annual thereafter.
Transition probabilities/ event rates	Treatment effects based on Study 108
	Baseline ppFEV ₁ decline based on large longitudinal registry analyses.
	Changes in treatment effect over time based on extension study PROGRESS (which studied lumacaftor/ivacaftor for patients homozygous for the F508del mutation) and large longitudinal registry analyses.
	Baseline hazard function derived survival data from Irish CF data registry.
Utilities	Survival was modelled using Liou CPH model (Liou et al 2001).
	Derived from a clinician survey: Normal=0.98, Mild=0.88, Moderate=0.67, Severe=0.37. Patients with lung transplant=0.81 (Anyanwu et al 2002)

Abbreviations: ACFDR, Australia Cystic Fibrosis Disease Registry; CEA, cost effectiveness analysis; CF, cystic fibrosis; CUA, cost utility analysis; LYGs, life years gained; QALYs, quality adjusted life years; RF, residual function

Source: Table 3.1.1, p. 180 of the Submission.

6.29 The economic model included the baseline risk profiles from individual patients aged 12 years and over from Study 108, irrespective of treatment group. The applicability of the model to the Australian patient population was unclear. The evaluation considered that the RF mutation patient population included in the model could have been obtained from the Australian Cystic Fibrosis Data Registry (ACDFR).

6.30 To determine the baseline hazard function, a Gompertz parametric distribution was applied to extrapolate data from the Kaplan-Meier (KM) curve of Irish registry patients. The hazard was then adjusted based on individual patient characteristics and risk factors (ppFEV₁, weight-for-age z-score, pancreatic sufficiency, diabetes mellitus, S. aureus, B. cepacia, annual number of acute pulmonary exacerbations, pulmonary exacerbations × B. cepacia) for patients in Study 108. It was noted during the evaluation that the entire Irish CF registry was used rather than the subset of patients with the RF mutation. In the PSCR it was argued that the adjustment to the hazard for the entire registry population using the characteristics of patients in Study 108 accounted for the expected mortality difference for patients with the RF mutation compared with the total population. The ESC considered it was unclear if the adjustment adequately accounted for the mortality difference and hence if the

baseline hazard in the model reflects that for patients with the RF mutation. The ESC noted the adjustment increased the median survival from 39.9 years for the entire Irish cohort to 41.3 years. As noted above, compared with patients who are homozygous to the CFTR F508del mutation, studies have shown that heterozygous patients have a better prognosis, and this is consistent with the predicted increase in survival. However, for all CF patients in Australia the median age at death was 32.6 years in 2016 (Australian Cystic Fibrosis Data Registry (ACFDR) 2016). The ESC has previously expressed doubt as to whether the use of the Irish registry accurately reflects the current survival in the Australian CF population (lumacaftor/ivacaftor PSD July 2017, paragraph 6.48), and the applicability of those data may be reduced further when applying it to patients with an RF mutation. The pre-PBAC response argued that “the median age at death derived in the ACFDR 2016 is by its nature based on an older birth cohort (which may have a shorter life expectancy) than would be expected in the prospectively modelled analysis...i.e. the ACFDR median age of death is not the same as the expected survival of current patients going forward”.

- 6.31 Overall, the submission used the same model structure and similar inputs as has been applied in previous submissions for CFTR modulators in CF but in the relevant setting (CF patients with an RF mutation). The PBAC has previously expressed a preference for modifications to the structure and inputs of that model (lumacaftor/ivacaftor (aged 12+ years) PSD July 2018, paragraph 6.52). The ESC considered that many of these modifications were also relevant to the application of the model to the RF treatment setting, as outlined in the paragraphs below and in Table 9.
- 6.32 The model incorporated a 42% decrease in the rate of decline in ppFEV₁ for tezacaftor/ivacaftor patients beyond the 8-week trial period to a lifetime time horizon (13.5 years on average), relative to BSC. This decline was informed by the longer-term ppFEV₁ data from the extension trial PROGRESS (of lumacaftor/ivacaftor in patients homozygous for the F508del mutation) compared with a matched control group. The evaluation noted that, while this decrease in the rate of decline was effectively accepted for lumacaftor/ivacaftor, this was in the context that a Managed Access Program (MAP) could be agreed with the Sponsor that included this 42% decrease as part of the performance criteria (lumacaftor/ivacaftor (aged 12+), PSD July 2018 paragraph 6.75). However, as a MAP was not proposed for tezacaftor/ivacaftor, the inclusion of a 42% decrease in the rate of decline in ppFEV₁ in the economic model was not appropriate. The PSCR stated that uncertainty surrounding this estimate is dealt with via the lumacaftor/ivacaftor MAP. Subsequent to the PSCR, the sponsor proposed that the outcome of the lumacaftor/ivacaftor MAP for patients homozygous for the F508del mutation be applied to the subsidisation caps for tezacaftor/ivacaftor for both of the requested indications. The ESC nevertheless considered that the assumption of a 42% decrease in the rate of decline in ppFEV₁ in the homozygous F508del mutation population was not justified for this patient population given the uncertainty around the long-term efficacy of tezacaftor/ivacaftor for the RF mutation patient population. Further, the ESC considered that the evidence presented did not adequately support the assumption of a lifetime treatment effect in the model. In this

regard, the ESC considered that assuming a rate of decline for tezacaftor/ivacaftor equal to BSC after the trial period may still favour tezacaftor/ivacaftor as patients treated with the intervention would always maintain the 6.8 percentage point difference in ppFEV₁ observed at week 8 in Study 108; the difference in ppFEV₁ may in fact reduce over the long term.

- 6.33 The model assumed a reduction in pulmonary exacerbation-related hospitalisation costs. The ESC noted that the model assumed this benefit based on non-statistical differences in the rates of pulmonary exacerbations between tezacaftor/ivacaftor and BSC in Study 108 (see paragraph 6.12) which may not have been appropriate. The pre-PBAC Response noted that while the rate of pulmonary exacerbations was not statistically significant, the lower rate of pulmonary exacerbations in the tezacaftor/ivacaftor arm was maintained through extension Study 110 whereas the rate of pulmonary exacerbations in the placebo arm increased. The pre-PBAC Response further noted that the model only captures pulmonary exacerbations that require hospitalisation or treatment with IV antibiotics and therefore would underestimate the annual rate of all pulmonary exacerbations.
- 6.34 The submission's base case assumed the annual cost of tezacaftor/ivacaftor based on the intended annual price of \$ [REDACTED] per patient, a 5% statutory price reduction and a further [REDACTED]% percentage reduction following loss of exclusivity. The list price should have been used, in line with the PBAC Guidelines and previous PBAC statements for other CFTR modulators (lumacaftor/ivacaftor (aged 12+), PSD July 2018 paragraph 6.52). The PSCR argued "these price changes mark real and significant decreases in future costs that may be borne by the Australian Government, and therefore, should be included in the analysis". The ESC considered that including these price reductions in the model was inappropriate and inconsistent with the PBAC Guidelines. Furthermore, the ESC disagreed with the PSCR that these price changes represent real decreases in future costs and considered these price changes were unlikely to be realised in practice for the following reasons:
- As tezacaftor/ivacaftor is likely to be replaced with triple therapy and other "next generation correctors" over the next several years, it is unlikely that tezacaftor/ivacaftor will be widely used at the time that the submission assumed the price will reduce by [REDACTED] %.
 - The 5% and [REDACTED] % price reductions in the model were applied to the intended annual price of \$ [REDACTED] per patient; however, the 5% statutory price reduction would apply to the requested ex-manufacturer price of \$21,000 (or around \$270,000 per patient per year). Furthermore, there is a significant risk that the Government would pay a higher amount than the intended price of \$ [REDACTED] per patient per year (see below paragraph) and the terms of the current Deed of Agreement, including the subsidisation caps and intended resulting price per patient, may not apply when generic versions of tezacaftor/ivacaftor become available.
- 6.35 Table 9 outlines the parameter changes to the submission base case that ESC thought were most appropriate for PBAC decision making. While the ESC noted that the

submission was proposing an intended annual price of \$ [REDACTED] per patient, it reiterated its view that there was a significant risk that the Government would pay a higher amount than this, as realisation of this price through subsidisation caps is dependent on estimated utilisation being achieved. Accordingly, given the uncertainty in the utilisation estimates, the ESC advised it would be informative to consider a range of ICERs using the parameter changes outlined in Table 9 at \$ [REDACTED] per patient per year and the requested list price. In this regard, the ESC considered the incremental cost effectiveness of tezacaftor/ivacaftor for the RF mutation population would likely be between more than \$200,000/QALY and more than \$200,000/QALY gained (see Table 10), with cost effectiveness being at the lower end of this range if the estimates of utilisation for tezacaftor/ivacaftor are met. Similarly, the ESC noted that the incremental cost effectiveness ratio would be better (lower) than more than \$200,000/QALY gained if the estimates of utilisation for tezacaftor/ivacaftor were exceeded; however, the ESC considered this outcome was less likely (see *Estimated PBS usage & financial implications*)

Table 9: Parameter changes in the ESC base case

Analysis description	Submission base case	ESC base case
Decrease in the decline in ppFEV ₁ following the trial period, relative to BSC	42%	0% (i.e. equivalent to BSC)
Reduction in PEx	45% reduction*	0% reduction
F1 5% statutory price and generic price reduction	5%	0%
Percentage reduction in cost following loss of exclusivity	[REDACTED]%	0%

Abbreviations: BSC= best supportive care; CF= cystic fibrosis; CI= confidence interval; FEV₁= forced expiratory volume in 1 second; LoE= loss of exclusivity; PEx= pulmonary exacerbations.

* The submission (p198) applied a rate ratio of 0.55 to the annual rate of PEx for patients treated with tezacaftor/ivacaftor. However, the rate ratio from Study 108 was 0.54, 95% CI 0.26, 1.13 (Study 108 CSR, p85 and pages 24, 165, and 172 of the submission).

Table 10: Results of the economic evaluation

Component	Tezacaftor/ivacaftor	BSC	Increment
Submission base case			
Costs	[REDACTED]	[REDACTED]	[REDACTED]
QALYs	8.82	6.38	2.44
Incremental cost/QALY gained			[REDACTED]
ESC base case* at the requested list price of \$273,938/patient/year			
Costs	[REDACTED]	[REDACTED]	[REDACTED]
QALYs	7.95	6.38	1.57
Incremental cost/QALY gained			[REDACTED]
ESC base case* with intended price of \$ [REDACTED] /patient/year through an RSA			
Costs	[REDACTED]	[REDACTED]	[REDACTED]
QALYs	7.95	6.38	1.57
Incremental cost/QALY gained			[REDACTED]

Abbreviations: BSC = best supportive care; QALY = quality-adjusted life-year; RSA = risk sharing arrangement.

Source: Table 3.7.5, p209 of the submission and calculated using the submissions Section 3 economic model.

*ESC base case as per the parameter changes in Table 9.

The redacted table shows ICERs in the range of more than \$200,000/QALY.

6.36 The key drivers of the model are summarised in Table 11.

Table 11: Key drivers of the model

Description	Method/Value	Impact
Intended price plus price reductions	Intended annual price of \$█████ per patient, implemented through subsidisation caps, applied for tezacaftor/ivacaftor drug cost. List price was considered.	High, favours tezacaftor/ivacaftor
Extrapolation of ppFEV ₁	Treatment effect continued beyond trial period (8 weeks) for life time. Lumacaftor/ivacaftor extension study PROGRESS (for F508del homozygous patients) was used to extrapolate beyond the trial period.	High, favours tezacaftor/ivacaftor
Modelled ppFEV ₁ decline after trial period	Annual decrease in the rate of decline in ppFEV ₁ was implemented relative to BSC (42%).	High, favours tezacaftor/ivacaftor
Extrapolation of survival	Liou et al (2001), extrapolation of treatment effect of intermediate outcomes on survival.	High, favours tezacaftor/ivacaftor
Treatment effect on PEx	The model assumed a benefit based on non-statistical differences between tezacaftor/ivacaftor and BSC. No treatment effect in terms of PEx reduction was assessed in a SA (RR = 1)	High, favours tezacaftor/ivacaftor

Abbreviations: BSC = best supportive care; PE = pulmonary exacerbation; ppFEV₁= per cent predicted forced expiratory volume in one second; RR= risk ratio; SA= sensitivity analysis

Source: compiled during the evaluation.

6.37 Results of the univariate sensitivity analysis (Table 12) showed that the greatest variation in the ICER occurred when it was assumed that there were no price reductions (as per PBAC Guidelines) resulting in a cost per QALY gained of more than \$200,000 (█████% increase from baseline). The next most influential was the scenario that assumed an annual ppFEV₁ decline equivalent to BSC after the trial period, resulting in an ICER of more than \$200,000/QALY (█████% increase). The results were also sensitive to assuming there was no treatment effect on the occurrence of pulmonary exacerbations (RR = 1; ICER=more than \$200,000/QALY).

Table 12: Results of sensitivity analyses that result in variations greater than 10%

Analysis description	Incremental cost (\$)	Incremental effect (QALYs)	ICER (\$/QALY)	% Variation
Base case	████████	██	████████	██
Discount rates				
Costs and benefits 0%	████████	██	████████	████%
Costs and benefits 1.5%	████████	██	████████	████%
Costs and benefits 3%	████████	██	████████	████%
Costs/prices				
Effective cost of tezacaftor/ivacaftor -10%	████████	██	████████	████%
Effective cost of tezacaftor/ivacaftor +10%	████████	██	████████	████%
Cost of BSC/disease management removed for the period of survival generated by tezacaftor/ivacaftor treatment	████████	██	████████	████%
Cost of PEx halved	████████	██	████████	████%
Cost of PEx doubled	████████	██	████████	████%
Effects				
Set annual decline in FEV ₁ in tezacaftor/ivacaftor-treated patients to 25% of BSC	████████	██	████████	████%
Set annual decline in FEV ₁ in tezacaftor/ivacaftor-treated patients to 75% of BSC	████████	██	████████	████%
PEx reduction due to tezacaftor/ivacaftor treatment increased by 0.20 (rate ratio = 0.35 [65% reduction])	████████	██	████████	████%
PEx reduction due to tezacaftor/ivacaftor treatment decreased by 0.20 (rate ratio = 0.75 [25% reduction])	████████	██	████████	████%
████████████████████				
Time horizon: life time – 1 year	████████	██	████████	████%
Decline in ppFEV ₁ 100% of BSC after trial period	████████	██	████████	████%
No treatment effect in terms of PE reduction due to tezacaftor/ivacaftor (RR = 1)	████████	██	████████	████%
No Tezacaftor/ivacaftor price reduction*	████████	██	████████	████%

Abbreviations: BSC= best supportive care; CF= cystic fibrosis; CI= confidence interval; FEV₁= forced expiratory volume in 1 second; ICER= incremental cost effectiveness ratio; LoE= loss of exclusivity; NA= not applicable; PEx= pulmonary exacerbation; QALY= quality adjusted life years.

Note: * Uses annual price by applying the list price (DPMQ of \$21,000), removes statutory price and generic reductions and no LoE reductions during for years 1 and 2.

Source: Table 3.8.1, p. 210 of the submission, additional analyses were included as part of the evaluation.

The redacted table shows ICERs in the range of \$75,000/QALY – more than \$200,000/QALY.

Drug cost/patient/year

6.38 The proposed published price in the submission was \$21,000 per 28-day pack resulting in a per year cost of \$273,938 (\$21,000/56 tablets per pack*2 tablets per day*365.25 days per year). The submission proposed an intended annual price of \$████████ per patient for tezacaftor/ivacaftor to be implemented through subsidisation caps through a Risk Sharing Arrangement. The proposed published price is higher than that for lumacaftor/ivacaftor (DPMQ of \$18,750 for Section 100 (Highly Specialised Drugs

Program) – public hospital) for patients aged ≥6 years who are homozygous for the F508del mutation.

Estimated PBS usage & financial implications

6.39 The submission was not considered by DUSC. An epidemiological approach was adopted. The submission acknowledged there is some uncertainty given the rarity of the condition. The submissions’ estimates of patient numbers, use and cost to the PBS are summarised in Table 13.

Table 13: Estimated use and financial implications

Description	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	■	■	■	■	■	■
Total number of packs dispensed per year	■	■	■	■	■	■
Estimated financial implications of tezacaftor/ivacaftor						
Gross PBS cost (without Cap)	■	■	■	■	■	■
Gross PBS cost (with Cap)	■	■	■	■	■	■
Total patient co-payment	■	■	■	■	■	■
Net cost to Government PBS (without financial cap)	■	■	■	■	■	■
Net cost to Government PBS (with financial cap)	■	■	■	■	■	■
Net Financial implications						
Net cost to the MBS	■	■	■	■	■	■
Overall impact on PBS/MBS (without Cap)	■	■	■	■	■	■
Overall impact on PBS/MBS (with Cap)	■	■	■	■	■	■

Abbreviations: IVA= ivacaftor; PBS= Pharmaceutical Benefit Scheme; RPBS= Repatriation Pharmaceutical Benefits Scheme
 Source: Table 4.2.11, p. 223 of the submission.

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 and the net cost to the PBS/MBS would be \$10 - \$20 million (without Cap) and less than \$10 million (with Cap).

6.40 The submission stated there are no currently reimbursed therapies that can be directly substituted because of tezacaftor/ivacaftor becoming PBS-listed. This was appropriate. However, over the mid- to long-term, treatment with tezacaftor/ivacaftor may reduce the need for some supportive therapies. Due to a lack of information in this regard, the submission assumed that there would be no reduction to PBS costs due to the reduction of concomitant therapies or other PBS medicines. This was consistent with the previous submission for lumacaftor/ivacaftor for patients who are homozygous for the F508del mutation.

- 6.41 The submission included the non-PBS related government health services likely to be impacted by the proposed listing of tezacaftor/ivacaftor on the PBS including: (1) MBS services for increased liver function tests (LFTs); (2) MBS services for ophthalmological visits; (3) reduced transplantation costs. The latter was not considered in the financial estimates. The evaluation considered this was appropriate.
- 6.42 The submission likely overestimated drug utilisation each year on the basis that:
- The submission assumed that no patients discontinued tezacaftor/ivacaftor after the initial 8 weeks of therapy. This was not adequately justified. The final PROGRESS study report indicates that 14.9% of the Final Analysis Set for this study discontinued study treatment because of an “adverse event” or “subject refused further dosing” (PROGRESS study report Version 1.0, 25 October 2016, pp 78).
 - The submission assumed that all patients initiate treatment from the first day of the first year of treatment. Previously, the PBAC noted that underestimation of discontinuation and assuming patients received a full year of treatment in their first year would result in an over-estimate of use: “A more reasonable assumption was that initiating patients would commence treatment throughout the year, so that on average each patient received the equivalent of half of a year’s supply in the year in which they commence treatment” (lumacaftor/ivacaftor (12+ years) PSD July 2018, paragraph 6.68). The submission did not incorporate this suggestion.
 - A treatment adherence rate of 80% was assumed. This number was obtained from the compliance rate in Study 108 with some adjustment for real-world setting. The same approach was adopted in previous submissions. The DUSC review of ivacaftor (DUSC February 2018, p. 1-13) noted that use was higher than expected, even though patient numbers were lower than estimated. This suggests that trial-based compliance may underestimate real-world use in this setting. While this factor may underestimate utilisation, the net overall impact of these uncertainties was a likely overestimation of utilisation.

The PSCR stated that the sponsor will work with the Department to finalise patient and script numbers to cater for half-years and variable discontinuation rates over time.

Quality Use of Medicines

- 6.43 The submission did not present any information with respect to the 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 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.”

- 6.44 The ESC considered that an additional quality use of medicines issue is the adjustment required when patients are co-prescribed a moderate or strong CYP3A inhibitor.

Financial Management – Risk Sharing Arrangements

- 6.45 The submission proposed a substantial reduction in the gross cost of tezacaftor/ivacaftor to the PBS via a subsidisation cap, to be implemented through a Risk Sharing Arrangement (RSA), in line with lumacaftor/ivacaftor for patients who are homozygous for the F508del mutation. The economic evaluation and financial estimates used the intended annual price of \$ [REDACTED] per patient.
- 6.46 In estimating the financial impact to the PBS with the proposed cap (per Table 13 above), the submission applied a relative cost reduction per patient of [REDACTED]%, rather than the annual price (of \$ [REDACTED] per patient). The [REDACTED]% rebate aligns with the rebate needed to achieve the intended annual price of \$ [REDACTED] per patient for lumacaftor/ivacaftor, based on the published DPMQ of \$18,750. As the current submission proposed a DPMQ for tezacaftor/ivacaftor of \$21,000, a higher rebate would be required to achieve the intended annual price of \$ [REDACTED] per patient. The pre-PBAC response noted that the submission incorrectly calculated the annual financial caps for the RF population and presented revised annual caps for the gross cost the PBS based on the intended annual price of \$ [REDACTED] per patient.
- 6.47 The use of an RSA to achieve an “effective price per patient” is associated with a significant risk that the Government would pay a higher amount than the intended price of \$ [REDACTED] per patient per year, as achieving this price through a subsidisation cap is dependent on the achievement of the estimated utilisation. The ESC noted that this approach may be less appropriate in this setting than for patients homozygous for the F508del mutations as the utilisation estimates are potentially more uncertain given the rarity of the RF mutations and that the submission likely overestimated drug utilisation each year (see paragraph 6.42). The ESC also noted that the higher DPMQ leads to a greater level of risk that the annual price of \$ [REDACTED] per patient would not be achieved in practice. The ESC considered that a more appropriate approach of using a Special Pricing Arrangement to achieve the cost-effective per patient price and an RSA to cap overall expenditure to manage the fiscal risk to Government.

Estimated Government expenditure per patient for Year 1 of listing for lumacaftor/ivacaftor

- 6.48 The PSCR stated “even though only listed in October 2018, Orkambi® [lumacaftor/ivacaftor] use alone is predicted to exceed the [subsidisation] cap, and therefore it is highly likely that even an increased cap would be readily exceeded”. The ESC noted that exceeding the subsidisation cap would not be sufficient to achieve the intended price per patient; rather, the estimated patient numbers for each year that were used to determine the subsidisation caps would need to be met. 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.

- 6.49 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 14). Table 15 presents the number of prescriptions and government expenditure for lumacaftor/ivacaftor for the first four months of listing.

Table 14: Subsidisation caps for lumacaftor/ivacaftor by year of listing

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

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

*Assuming 11 prescriptions per FTE patient per year.

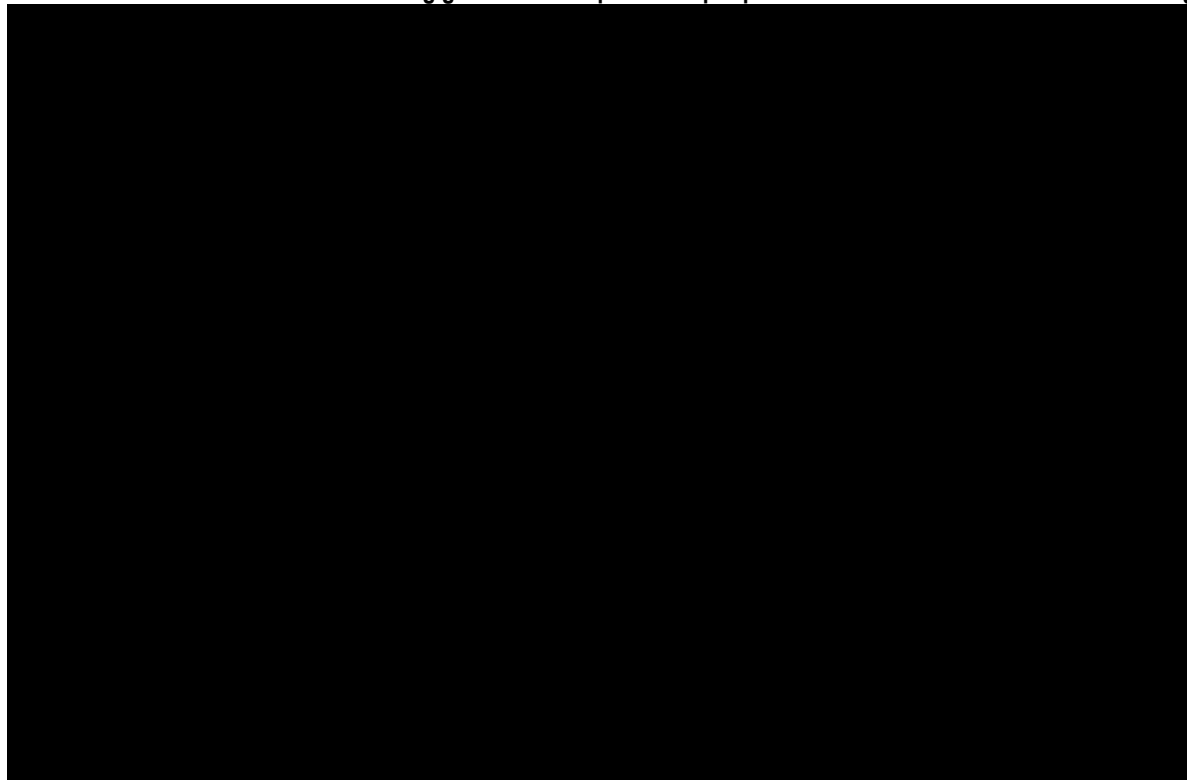
Table 15: Utilisation of lumacaftor/ivacaftor (by month of processing), October 2018 to January 2019

	Oct 2018	Nov 2018	Dec 2018	Jan 2019	Total
Prescriptions	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Government Expenditure	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

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

- 6.50 Figure 5 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, in which less than 10,000 patients are treated in February 2019 and for the remainder of Year 1, Government expenditure per patient would be around \$ [REDACTED] – higher than the intended annual price of \$ [REDACTED] per patient.

Figure 5: 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.

- 6.51 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.
- 6.52 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).
- 6.53 The PBAC considered that the lower than expected rate 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 6.2). 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.

- 6.54 The PBAC considered there was a significant risk that the proposed annual price per patient of \$ [REDACTED] for tezacaftor/ivacaftor for the RF mutation patient population would not be achieved through the proposed subsidisation caps through an RSA, particularly given the uncertainty around estimated utilisation given the rarity of the condition.

Managed Access Program (MAP)

- 6.55 In its consideration of lumacaftor/ivacaftor for patients aged ≥ 12 years who are homozygous for the F508del mutation, the PBAC considered that the cost-effectiveness of lumacaftor/ivacaftor would be acceptable if a MAP (along with other measures) were implemented. The PBAC considered that a MAP would allow patients to access treatment through the PBS whilst providing the sponsor with an extended period to provide further data to satisfy the PBAC that the benefits of treatment are sustained over a longer period (lumacaftor/ivacaftor (12+ years), July 2018 PSD paragraphs 7.3 and 6.73). The PBAC PSD states that, under the MAP, “subsidy could be paid at the sponsor’s asking price of \$ [REDACTED] per patient per year for a period of 2.5 years to allow the sponsor to provide further data to satisfy the PBAC that the differences in the rates of decline in lung function (ppFEV₁) 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 2.5 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 the PBAC considered that the price paid for lumacaftor with ivacaftor should reduce to a level consistent with the evidence provided” (July 2018 PSD, paragraphs 6.74 and 6.75).
- 6.56 The submission did not propose a similar MAP for tezacaftor/ivacaftor, despite the clinical data being subject to more uncertainty around the longer-term impact on lung function, compared with previous submission for lumacaftor/ivacaftor. The evaluation acknowledged that a MAP may be more difficult to implement in this circumstance given the efficacy data for tezacaftor/ivacaftor are based on a shorter duration of follow-up (8 weeks plus 24 weeks of extension data) than those for lumacaftor/ivacaftor (24 weeks plus 96 weeks of extension data). Further, the patient numbers are likely to be smaller and thus the necessary patient follow-up data may be more limited.
- 6.57 The PSCR requested that tezacaftor/ivacaftor patients should not be included “in the actual MAP data collection process *per se* particularly given that the earliest possible listing date for tezacaftor/ivacaftor is one year into the MAP follow-up period. Furthermore, inclusion of the tezacaftor/ivacaftor-treated RF patients is particularly problematic due to relatively small number of these patients and the heterogeneity of the groups – therefore considerably increasing the chance of a spurious finding (in

either direction)". 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 ppFEV₁ 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). The ESC considered that applying the result of the lumacaftor/ivacaftor MAP for the homozygous F508del population alone would not address the uncertainty in the long-term effectiveness of tezacaftor/ivacaftor for the RF mutation population.

- 6.58 The PBAC noted that the submission did not propose a MAP similar to which currently applies to lumacaftor/ivacaftor. However, the PBAC considered that a similar MAP might not adequately address the uncertainty around the longer-term efficacy of tezacaftor/ivacaftor as the operation of the MAP requires the availability of longer-term data, which may be limited in the context of this rare condition. In the absence of longer-term data for tezacaftor/ivacaftor for this patient population, the PBAC pragmatically advised that should the MAP for lumacaftor/ivacaftor result in any change to the lumacaftor/ivacaftor price per patient per year, this price should also be applicable to the listing of tezacaftor/ivacaftor for the RF mutation patient population.

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 for the treatment of patients aged 12 years or older who have one copy of the F508del mutation and another residual function (RF) mutation in the CFTR gene, on the basis that it should be available only under special arrangements under Section 100 (Highly Specialised Drugs Program). The PBAC is satisfied that tezacaftor/ivacaftor provides, for some patients, a significant improvement in efficacy over best supportive care (BSC). The PBAC recommended the special arrangements and circumstances described in the tables in section 8 below.
- 7.2 The PBAC considered that the restriction should restrict use to RF mutation patients who have one copy of the F508del mutation in the CFTR gene in line with the patient population in the clinical trial, Study 108. The list of approved RF mutations is as defined in Table 1 of the TGA approved product information for tezacaftor/ivacaftor.
- 7.3 The PBAC noted the many consumer comments and correspondence from Cystic Fibrosis Australia in support for subsidised access to tezacaftor/ivacaftor for CF patients with these rare mutations. The PBAC noted that the consumer comments indicated that patients and their families perceive that treatment with tezacaftor/ivacaftor (and other CFTR modulators) will be associated with a range of potential benefits (see paragraph 6.3).

- 7.4 The PBAC accepted that BSC was the appropriate main comparator for the requested population.
- 7.5 The PBAC noted the primary outcome from Study 108, of absolute change from baseline in ppFEV₁, indicated a statistically significant increase in ppFEV₁ for patients treated with tezacaftor/ivacaftor compared with BSC of 6.8% (95% CI: 5.7, 7.8) after 8 weeks of treatment. The interim analysis of extension data from Study 110 indicated that the absolute change from baseline in ppFEV₁ observed in the tezacaftor/ivacaftor group after 8 weeks of treatment in treatment period 2 of Study 108 was maintained for an additional 16 weeks of treatment (i.e. up to 24 weeks of continuous treatment). However, the PBAC considered that the crossover design of Study 108 may have confounded the comparison to Study 110 (see paragraph 6.8). Overall, the PBAC considered the claim of superior efficacy compared with BSC was adequately supported in the short-term; however, the PBAC noted that given the short duration of follow-up, it was unknown whether the observed improvement in ppFEV₁ would be maintained in the long-term, particularly in the context of a lifelong progressive disease. The PBAC considered the long-term effectiveness of tezacaftor/ivacaftor for this patient population was even more uncertain than the evidence for lumacaftor/ivacaftor for the F508del homozygous population (with 24 weeks in TRAFFIC/TRANSPORT plus 96 weeks of extension data from PROGRESS for lumacaftor/ivacaftor and 24 weeks from EVOLVE plus 24 weeks of extension data from Study 110 for tezacaftor/ivacaftor).
- 7.6 The PBAC was also uncertain that the magnitude of treatment effect was representative of the likely clinical benefit across the group of requested RF mutations given the potential variability of treatment outcomes between patients with different RF mutations. The PBAC noted that not all known RF mutations have clinical data to suggest a positive clinical benefit and of those RF mutations included in Study 108, each was associated with ≤ 21 patients. Given the rarity of the RF mutations, however, the PBAC acknowledged that more reliable clinical data from studies with adequate power to assess the impact of treatment across all RF mutations would not be forthcoming.
- 7.7 The PBAC noted that Study 108 found an improvement in quality of life, as measured by the CFQ-R Respiratory Domain Score, compared with BSC after 8 weeks of treatment; however, it was uncertain whether this difference would be maintained over the long-term. The difference in the rate of pulmonary exacerbations was lower for tezacaftor/ivacaftor than for placebo (6.8% and 11.8% respectively); however, the difference in event rates was not statistically significant (RR: 0.54; 95% CI 0.26-1.13). There was insufficient clinical evidence to determine if treatment with tezacaftor/ivacaftor for the RF mutation patient population would be associated with improvements in life expectancy, nutritional status (including weight and height) or reduction in need for other medications. However, the PBAC acknowledged the high clinical need for therapy for this patient population and considered there is a clinical place for this medicine at a price commensurate with its potential clinical benefits.

- 7.8 Given the short duration of the trial, the PBAC considered there were insufficient data to adequately evaluate the safety of tezacaftor/ivacaftor in this patient population. However, the PBAC noted there were no major safety signals for tezacaftor/ivacaftor in the context of the known safety profiles of other CFTR modulators.
- 7.9 The PBAC noted the economic model presented had the same structure as that for previous CFTR modulator submissions. The PBAC noted the decrease in the rate of decline in ppFEV₁ of 42% applied in the model was based on longer-term data from the lumacaftor/ivacaftor PROGRESS study for patients homozygous for the F508del mutation, compared with a matched historical control cohort, and therefore may not reflect the decrease in the rate of decline that would occur for the RF mutation population. Further, the PBAC recalled it previously considered this assumed rate of decline to be overly optimistic, noting that lumacaftor/ivacaftor was recommended using this estimate on the basis that (among other factors) a MAP would apply to ensure that the price paid was consistent with the evidence (see paragraph 6.55). The PBAC also noted that the base case ICER inappropriately included 5% statutory price reductions and a [REDACTED] % price reduction for loss of exclusivity from the intended annual price of \$ [REDACTED] per patient, which may not be achieved. The PBAC also noted that the economic model did not include the significant hospital resources that may be required to initiate patients on tezacaftor/ivacaftor, in line with the clinical protocol for initiation of lumacaftor/ivacaftor that was described by the clinician during the sponsor hearing (see paragraph 6.2). Overall, the PBAC considered that the base case ICER presented in the submission was uninformative for decision making.
- 7.10 The PBAC acknowledged that more reliable data regarding the decrease in the rate of decline in ppFEV₁ associated with treatment with tezacaftor/ivacaftor (as well as other clinical benefits) for this patient population are unlikely to become available. Accordingly, the PBAC pragmatically considered that the ICER for tezacaftor/ivacaftor for the RF mutation patient population would likely be no higher than that for lumacaftor/ivacaftor for the F508del homozygous patient population if the price for tezacaftor/ivacaftor was no higher than the price previously recommended for lumacaftor/ivacaftor (of \$ [REDACTED] per patient per year). The PBAC further advised that tezacaftor/ivacaftor should be listed with a published DPMQ no higher than that for lumacaftor/ivacaftor.
- 7.11 The PBAC considered that the submission's estimate of utilisation of tezacaftor/ivacaftor for this patient population was uncertain and likely overestimated, for the reasons outlined in paragraph 6.42. The PBAC was of the view that the RF mutation patient population should be included in the existing lumacaftor/ivacaftor Deed of Agreement and any change to the lumacaftor/ivacaftor price per patient per year as a result of the MAP should also be applicable to the price of tezacaftor/ivacaftor, in order to manage the uncertain cost-effectiveness of tezacaftor/ivacaftor in this treatment setting.
- 7.12 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. In this regard, the PBAC advised that any increase to the existing financial caps for lumacaftor/ivacaftor to include patients with an RF mutation would need to account for the difference between the expected and actual utilisation of lumacaftor/ivacaftor in the homozygous F508del population. Given that uptake of lumacaftor/ivacaftor appears significantly lower than estimated utilisation in July 2018, it may be appropriate to include tezacaftor/ivacaftor for the treatment of the RF patient population to the existing financial caps for lumacaftor/ivacaftor without any increase. The PBAC considered that it may be appropriate for the Department to implement other measures to ensure tezacaftor/ivacaftor does not exceed the price of \$ [REDACTED] per patient per year; this could be achieved through a Special Pricing Arrangement, as per the July 2018 recommendation for lumacaftor/ivacaftor.

- 7.13 The PBAC considered it would be appropriate to include prescribing instructions in the tezacaftor/ivacaftor restriction specifying the dose adjustments required for patients who are concomitantly receiving a moderate or strong CYP3A inhibitor. 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.
- 7.14 The PBAC advised that tezacaftor/ivacaftor is not suitable for prescribing by nurse practitioners.
- 7.15 The PBAC recommended that the Early Supply Rule should apply.
- 7.16 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 Pharmaceuticals (Australia) Pty Ltd

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

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Restriction:	<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
Treatment criteria:	<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 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>
Clinical criteria:	<p>Patient must have one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor with ivacaftor; AND Patient must have one F508del mutation in the CFTR gene; AND The treatment must be given concomitantly with standard therapy for this condition.</p>
Population criteria:	<p>Patient must be 12 years of age or older.</p>
Prescriber Instructions:	<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, the list of mutations considered to be responsive to tezacaftor with ivacaftor is defined in the TGA approved product information.</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 or 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 (2) a completed Cystic Fibrosis Tezacaftor with Ivacaftor Authority Application Supporting Information Form; and and</p>

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	<p>(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</p> <p>(4) 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>(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>Administrative Advice:</p>	<p>Managed Access Program:</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 24 weeks of data for tezacaftor with ivacaftor for children aged 12 years and over, as well as on the basis of 96 weeks of data for lumacaftor with ivacaftor in children aged 12 years and over who are homozygous for the F508del mutation. Information about the long term benefits of this medicine and lumacaftor with ivacaftor for patients who are homozygous for the F508del mutation will be collected and analysed under this MAP. For more information on Managed Access Programs, please visit http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/2015-03/march-2015-other-matters-managed-access-programme-framework.</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 www.humanservices.gov.au</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 www.humanservices.gov.au</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>Category /</p>	<p>Section 100 – Highly Specialised Drugs Program</p>
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Program	
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Cystic Fibrosis
Treatment phase:	Continuing treatment
Restriction:	<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
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 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.
Population criteria	Patient must be 12 years of age or older.
Prescriber Instructions	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. 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. 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. Dosage of tezacaftor with ivacaftor is tezacaftor 100 mg/ivacaftor 150 mg twice weekly (approximately 3 or 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 Tezacaftor with ivacaftor is not PBS-subsidised for this condition in a patient who is currently receiving one of the following CYP3A4 inducers: Strong CYP3A4 inducers: avasimibe, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's wort Moderate CYP3A4 inducers: bosentan, efavirenz, etravirine, modafinil, nafcillin Weak CYP3A4 inducers: armodafinil, echinacea, pioglitazone, rufinamide. 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 Continuing Application Supporting Information Form; and

	<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>Administrative Advice:</p>	<p>Managed Access Program:</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 24 weeks of data for tezacaftor with ivacaftor for children aged 12 years and over, as well as on the basis of 96 weeks of data for lumacaftor with ivacaftor in children aged 12 years and over who are homozygous for the F508del mutation. Information about the long term benefits of this medicine and lumacaftor with ivacaftor for patients who are homozygous for the F508del mutation will be collected and analysed under this MAP. For more information on Managed Access Programs, please visit http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/2015-03/march-2015-other-matters-managed-access-programme-framework.</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 www.humanservices.gov.au</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 www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>

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.