

**5.04 LUMACAFTOR WITH IVACAFTOR,
lumacaftor 200 mg + ivacaftor 125 mg tablet, 4 x 28,
ORKAMBI®,
Vertex Pharmaceuticals Pty Ltd**

1 Purpose of Application

1.1 To request Section 100 (Highly Specialised Drugs Program), Authority Required listing for lumacaftor/ivacaftor fixed dose combination (FDC) for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
LUMACAFTOR + IVACAFTOR lumacaftor 200 mg + ivacaftor 125 mg tablet	112	5	\$ [REDACTED]	Orkambi®	VX

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
Condition:	Cystic fibrosis
PBS Indication:	Cystic fibrosis
Restriction Level / Method:	<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:	<i>Patient must be assessed through a cystic fibrosis clinic/centre which is under the control of specialist respiratory physicians with experience and expertise in the management of cystic fibrosis. If attendance at such a unit is not possible because of geographical isolation, management (including prescribing) may be in consultation with such a unit, AND Patient must be homozygous for the F508del mutation in the CFTR gene, AND The treatment must be given concomitantly with standard therapy for this condition.</i>
Population criteria:	<i>Patient must be 12 years of age or older.</i>

Prescribing instructions	<p>The authority application must be in writing and must include:</p> <p>(1) a completed authority prescription form; and</p> <p>(2) a completed Cystic Fibrosis Lumacaftor with Ivacaftor Authority Application Supporting Information Form; and</p> <p>(3) a signed patient acknowledgement; or an acknowledgement signed by a parent or authorised guardian, if applicable; and</p> <p>(4) a copy of the pathology report detailing the molecular testing for the patient being homozygous for the F508del mutation on the CFTR gene.</p>
Administrative advice	<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>

- 2.2 The requested PBS restriction did not specify the percent predicted FEV₁ (ppFEV₁) of patients. The efficacy and safety of lumacaftor/ivacaftor in patients with <40% and >90% ppFEV₁ was not evaluated in the clinical trials and is unknown.
- 2.3 The requested basis for listing is cost-effectiveness compared with the nominated comparator (best supportive care).

3 Background

- 3.1 The submission was made under TGA/PBAC Parallel Process. On 2 March 2016, the TGA delegate approved the registration of lumacaftor/ivacaftor.
- 3.2 Lumacaftor/ivacaftor FDC has not been considered by the PBAC previously.
- 3.3 The PBAC considered submissions for ivacaftor monotherapy for CF patients aged six years or older who have a G551D mutation in the CFTR gene in July 2013, November 2013, March 2014 and November 2014. The PBAC recommended listing for ivacaftor in March 2014, considering that the cost effectiveness would be acceptable if a 'pay for performance arrangement together with other risk sharing measures were adopted' (March 2014 PBAC PSD). Ivacaftor was listed on the PBS on 1 December 2014.

4 Clinical place for the proposed therapy

- 4.1 CF is an autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. CF is a progressive multi-organ disease that primarily affects the pulmonary and digestive systems.

- 4.2 It is proposed that lumacaftor/ivacaftor will be administered as an add on to current best supportive care.

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

5 Comparator

- 5.1 The nominated comparator was best supportive care. The ESC agreed this was the appropriate comparator given that neither drug as monotherapy has been shown to be effective for this patient population in clinical trials.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician presented an overview of the biological mechanisms underpinning cystic fibrosis, the factors of the disease which have been found to result in poorer health outcomes and the treatment goals in cystic fibrosis. The clinician further discussed how the drug would be used in practice, and addressed other matters in response to the Committee's questions. The PBAC considered that the hearing did not add substantively to the evidence presented in the submission.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (594), health care professionals (2) and organisations (6) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with lumacaftor/ivacaftor, including improvement in lung function, reduction in chest infections and exacerbations, weight gain, fewer hospital visits, fewer medications to be consumed on a daily basis, slowing disease progression and enabling stability of lung function, improving quality of life and enabling greater participation in society (including less time off work and school for illness). The comments noted that a small improvement in quality of life made a large difference to the life of patients. The comments also noted that lumacaftor/ivacaftor is a treatment which targets the underlying genetic defect which causes cystic fibrosis, rather than merely treating the symptoms of the disease.
- 6.3 The PBAC noted the advice received from Cystic Fibrosis Australia, Western Australia, Tasmania, South Australia and New South Wales and the Thoracic Society of Australia and New Zealand clarifying the likely use of lumacaftor/ivacaftor in clinical practice. The PBAC specifically noted the advice that lumacaftor/ivacaftor is a targeted therapy which may stabilise lung function, reduce hospitalisations and utilisation of other drugs, decrease morbidity and mortality and improve quality of life. The PBAC noted that this advice was supportive of the evidence provided in the submission.

- 6.4 Representatives of the PBAC met with Cystic Fibrosis Australia prior to the PBAC meeting, and reported the following key points to the PBAC in relation to this agenda item for the treatment of cystic fibrosis:
- CFA and patients believe that lumacaftor/ivacaftor is an essential medicine. Without PBS subsidised access, the cost of lumacaftor/ivacaftor would prohibit most patients from accessing the drug.
 - The symptoms of cystic fibrosis and the associated treatments, tests and hospitalisations limit the ability of this population of CF patients (and their carers) to participate in school, employment and the community. The CFA highlighted the physical, emotional and financial drain on patients, families and carers and the financial burden on state and federal health care and welfare systems associated with this condition. Everyday activities such as laughing or crying can provoke severe coughing fits. CF-related issues with adequate nutrition make eating a chore for patients. In a single year CF patients can require hundreds of hours of physiotherapy and medical appointments, hundreds of insulin injections and thousands of hours using a nebuliser. For children with CF frequent school absences can isolate a child from their peers. Adults with CF find employment opportunities curtailed due to the impacts of their disease.
 - CFA and patients have a strong sense of hope that lumacaftor/ivacaftor treatment will be associated with very good health and quality of life outcomes for some patients. The outcome of most importance to patients (and their families) was “general wellness” and the impact on quality of life and mental health. Other outcomes of importance included fewer admissions to hospital, fewer exacerbations, reduction in need for intravenous antibiotics, lung function and weight gain.
 - It was acknowledged that Lumacaftor/ivacaftor treatment for CF patients homozygous for the F508del mutation does not appear to be as effective as treatment with ivacaftor monotherapy (already subsidised on the PBS) for patients with G551D mutation or other gating (class III) mutation (particularly in terms of change in FEV₁). Regardless of the effect of the combination of ivacaftor/lumacaftor on FEV₁, CF patients believe that the benefits of the treatment are significant.
 - Other treatment options were also discussed but patients deemed these not to be as effective as lumacaftor/ivacaftor treatment and are more aimed at treating the symptoms rather than the underlying cause of the disease. The burden of these treatments was discussed, including the volume of medication, nutritional feed, constant admissions to the hospital and an associated potential for long-term trauma and side effects for the patient (e.g. body aches). Patients perceived that a benefit of lumacaftor/ivacaftor would be a reduction in the need for other treatments and hospitalisations.
 - The PBAC noted that the TGA has approved the registration of lumacaftor/ivacaftor for the treatment of cystic fibrosis in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene. The PBAC noted that it is aware of trials in younger children and queried whether there

would be any issues with restricting access on the basis of age, in line with the TGA registration. CFA indicated that listing lumacaftor/ivacaftor on the PBS for ages 12 and older would be for the good of the community.

Clinical trials

6.5 The submission was based on two head-to-head trials comparing lumacaftor/ivacaftor to placebo; Traffic (n=374) and Transport (n=374). Supportive evidence from one extension trial (Progress, n=516) was also presented.

6.6 Details of the trials presented in the submission are provided in the following table.

Table 1: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
Traffic	Clinical study report VX12-809-103 A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation	08 September 2014
Transport	Clinical study report VX12-809-104 A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation Wainwright CE, Elborn JS, Ramsey B, Marigowda G et al. Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR.	02 September 2014 NEJM 2015; 373:220-23
Supplementary randomised trials		
Progress	Clinical study report VX12-809-105 A Phase 3, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With Lumacaftor in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous or Heterozygous for the F508del-CFTR Mutation Interim analysis 2 (IA2) at Week 24 Elborn, J., Ramsey, B. and Boyle, M. B. Lumacaftor in combination with ivacaftor in patients with cystic fibrosis who were homozygous for the F508del-CFTR mutation.	18 May 2015 The 38th annual European Cystic Fibrosis Conference, Brussels, Belgium, 10-12 June 2015

Source: Table B.2.2, p56 of the submission

6.7 The key features of the direct randomised trials are summarised in the following table.

Table 2: Key features of the included evidence for lumacaftor/ivacaftor vs placebo

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Traffic	374 [^]	R, DB, MC 24 weeks	Low	Aged 12 or older Homozygous for the F508del mutation	Absolute change in ppFEV ₁ , BMI, CFQ-R, pulmonary exacerbations, EQ-5D-3L	Absolute change in ppFEV ₁ , weight for age z-score, pulmonary exacerbations
Transport	376 [*]	R, DB, MC 24 weeks	Low	Aged 12 or older Homozygous for the F508del mutation	Absolute change in ppFEV ₁ , BMI, CFQ-R, pulmonary exacerbations, EQ-5D-3L	Absolute change in ppFEV ₁ , weight for age z-score, pulmonary exacerbations

DB=double blind; MC=multi-centre; R=randomised; CFQ-R=cystic fibrosis questionnaire revised; BMI=body mass index

[^]n=374 in the 2 arms of the trial included in the analysis. The trial had a third arm (600 mg lumacaftor qd, 250 mg ivacaftor q12h) with n=185

^{*}n=376 in the 2 arms of the trial included in the analysis. The trial had a third arm (600 mg lumacaftor qd, 250 mg ivacaftor q12h) with n=187

Source: compiled during the evaluation

- 6.8 A greater proportion of patients had a ppFEV₁ of less than 70% in the clinical trials compared with the Australian CF population at baseline (71% vs 55%, respectively). Results of sub-group analyses from Traffic and Transport indicated that the magnitude of improvement in ppFEV₁ as a result of lumacaftor/ivacaftor treatment was smaller in those with a higher baseline ppFEV₁ (see the below table). The PSCR (p4-5) argued that the proportion of patients in the Australian CF population who had a ppFEV₁ of less than 70% was inclusive of all age groups, including children younger than 12 years; this is in comparison with the clinical trials, which only enrolled patients aged 12 years or over. The PSCR argued that as FEV₁ declines with age, the difference between the Australian CF population and the pivotal trials can be explained by the inclusion of children younger than 12. The ESC considered this was reasonable and likely to explain some of the difference in ppFEV₁.

Table 3: Results of absolute change from baseline in percent predicted FEV₁ by baseline FEV₁

	Traffic		Transport	
	LUM 400 mg q12h/ IVA 250 mg q12h (N=182)	Placebo (N=184)	LUM 400 mg q12h/ IVA 250 mg q12h (N=187)	Placebo (N=187)
PP FEV₁ at screening <70				
LS Mean (SE)	2.88 (0.624)	-0.07 (0.611)	2.63 (0.654)	-0.94 (0.664)
LS mean difference (95% CI)	2.95 (1.33, 4.57)		3.57 (1.89, 5.24)	
P value	0.0004		<0.0001	
PP FEV₁ at screening >70				
LS Mean (SE)	1.20 (1.050)	-0.99 (1.098)	2.68 (1.040)	1.06 (1.034)
LS mean difference (95% CI)	2.19 (-0.81, 5.19)		1.62 (-1.26, 4.50)	
P value	0.1506		0.2693	

Source: Table 11.27, p167 Traffic CSR and Table 11.28, p178 Transport CSR

Comparative effectiveness

6.9 The following table and figure present the results of the comparison of lumacaftor/ivacaftor versus placebo for the main outcome of absolute change from baseline in ppFEV₁.

Table 4: Results of absolute change in ppFEV₁ in the direct randomised trials

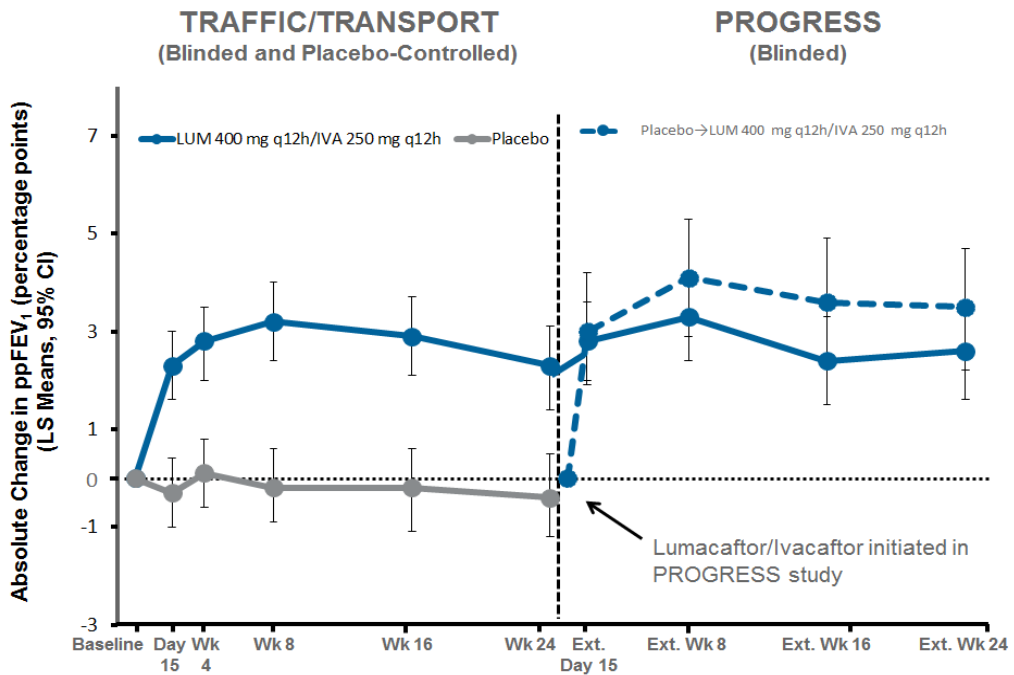
Trial ID	Lumacaftor 400 mg q12h/ Ivacaftor 250 mg q12h mean (SE)	Placebo mean (SE)	Mean difference [^] (95% CI)
Traffic	2.16 (0.530)	-0.44 (0.524)	2.60 (1.18,4.01)
Transport	2.85 (0.540)	-0.15 (0.539)	3.00 (1.56,4.44)
Pooled result	2.49 (0.379)	-0.32 (0.376)	2.81 (1.80,3.82)

Source: Table B.6.1, p 93 of the submission

Abbreviations: SE, standard error; CI, confidence interval; q12h, every 12 hours; qd, daily.

[^]Least squares mean difference

Figure 1: Absolute change from baseline in percent predicted FEV₁: Up to 48 weeks of treatment



Source: Figure B.7.2, p113 of the submission

6.10 The submission did not indicate what difference in ppFEV₁ was considered to be clinically meaningful, however the PBAC has previously defined the minimal clinically important difference (MCID) as an absolute change in ppFEV₁ of 10% (aztreonam PSD, July 2012). The PSCR (p1) argued that a comparison of the clinical significance of observed FEV₁ effect with aztreonam is not appropriate as aztreonam has a short-term effect. The ESC noted that the July 2013 ivacaftor monotherapy PBAC submission for use in cystic fibrosis patients with a G551D mutation

referenced the PBAC's acceptance of a MCID of 10% and that this was met with an improvement in ppFEV₁ of 10% from baseline in ivacaftor treated patients compared with best supportive care (BSC). The ESC considered that the 2.81% improvement was considerably smaller than the improvement of 10% demonstrated for ivacaftor monotherapy, and that the clinical significance of this improvement was highly uncertain.

- 6.11 The PSCR (p1-3) argued that the improvement in FEV₁ should not be considered in isolation, as lumacaftor/ivacaftor was intended to provide systemic benefits to the patient, including the prevention of pulmonary exacerbations and the improvement in nutritional status.
- 6.12 The ESC noted that lumacaftor/ivacaftor showed a numerical improvement over placebo in the secondary outcome measures in the Traffic and Transport trials (number of pulmonary exacerbations, BMI and CFQ-R). Statistically significant improvements were seen in the pooled analysis for the number of pulmonary exacerbations, weight for age z-score and BMI.
- 6.13 The ESC considered the incremental improvements (compared with placebo) demonstrated in patient's weight, ppFEV₁ and CFQ-R were more compelling for ivacaftor monotherapy than for lumacaftor/ivacaftor (see the below table).

Table 5: Selected comparison of incremental improvements (compared with placebo) for lumacaftor/ivacaftor(in F508del/F508del) and ivacaftor (in G551D)

Outcome	Lumacaftor/ivacaftor LSMD (95% CI)	Ivacaftor LSMD (95% CI)
ppFEV₁ : Absolute difference from baseline at 24 weeks	2.81 (1.80, 3.82)	10.58 (8.57, 12.59)
Weight : Absolute difference from baseline in weight-for-age z-score at week 24	0.0678 (0.0256, 0.1100)	0.319 (0.146, 0.492)
CFQ-R : Absolute difference from baseline in CFQ-R Respiratory Domain Score at Week 24	2.22 (-0.01, 4.45)	7.06 (3.66, 10.46)*

Source: Tables B.6.1, B.6.4, Table B.6.5 of the lumacaftor/ivacaftor March 2016 Commentary; Tables B.6.1, B.6.5, B.6.6 of the ivacaftor July 2013 Commentary (results from STRIVE trial); and Table B.6.9 of the ivacaftor July 2013 submission (results from STRIVE trial).

LSMD = least squares mean difference;

*Result for adolescents and adults – subjects 14 years and older. Pooled result for adolescents/adults and children was 8.08 (4.73, 11.42).

- 6.14 The ESC noted that while the impact of lumacaftor/ivacaftor on sweat chloride levels was investigated as part of a phase 2 trial, Study 102 (VX09-809-102), it was not investigated in the pivotal trials, Traffic and Transport. In Study 102, lumacaftor/ivacaftor led to a small but statistically significant reduction in sweat chloride levels of -9.8 mmol/L (P<0.001). The ESC considered that sweat chloride levels from Traffic and Transport would have been highly informative in demonstrating whether the lumacaftor/ivacaftor impacts the underlying biology of the disease. In this regard, the ESC noted that a statistically significant treatment effect of -47.9 mmol/L (P<0.001) between baseline and week 24, was associated with treatment with ivacaftor monotherapy, compared with placebo (Ramsey et al, 2011).
- 6.15 The PBAC also noted that, based on the pooled results from the Traffic and Transport trials, treatment with lumacaftor/ivacaftor was associated with statistically significant improvements in the following outcomes through to week 24:

- Number of pulmonary exacerbations (RR: 0.61; 95% CI: 0.49, 0.76).
- Number of pulmonary exacerbations requiring hospitalisation (RR: 0.39; 95% CI: 0.27, 0.56).
- Number of pulmonary exacerbations requiring intravenous antibiotic therapy (RR: 0.44; 95% CI: 0.32, 0.59).

In addition, the PBAC noted that the results from the extension study Progress suggested maintenance of the treatment effect on pulmonary exacerbations of lumacaftor/ivacaftor up to 48 weeks.

Comparative harms

- 6.16 A summary of the adverse events for lumacaftor/ivacaftor versus placebo is presented in the table below.

Table 6: Summary of adverse events in Traffic and Transport, safety set

AE Category	Traffic		Transport		Pooled	
	Lumacaftor 400 mg q12h/ Ivacaftor 250 mg q12h	Placebo	Lumacaftor 400 mg q12h/ Ivacaftor 250 mg	Placebo	Lumacaftor 400 mg q12h/ Ivacaftor 250 mg	Placebo
Total number of AEs	1019	994	1111	1138	2130	2132
Subjects with any AEs, n (%)	174 (95.6)	174 (94.6)	177 (94.7)	181 (97.3)	351 (95.1)	355 (95.9)
Subjects with AEs leading to treatment discontinuation, n (%)	6 (3.3)	4 (2.2)	11 (5.9)	2 (1.1)	17 (4.6)	6 (1.6)
Subjects with AEs leading to treatment interruption, n (%)	14 (7.7)	10 (5.4)	8 (4.3)	15 (8.1)	22 (6.0)	25 (6.8)
Subjects with SAEs, n (%)	33 (18.1)	49 (26.6)	31 (16.6)	57 (30.6)	64 (17.3)	106 (28.6)
Subjects with related SAEs, n (%)	8 (4.4)	3 (1.6)	6 (3.2)	5 (2.7)	14 (3.8)	8 (2.2)
Subjects with AEs leading to death, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Table B.6.4, p103 of the submission

Abbreviations: AE, adverse event; q12h, every 12 hours; qd, daily; SAE, serious adverse event.

Benefits/harms

- 6.17 A summary of the comparative benefits and harms for lumacaftor/ivacaftor versus placebo is presented in the following table.

Table 7: Summary of comparative benefits and harms for lumacaftor/ivacaftor and placebo

Benefits							
ppFEV ₁ : absolute change from baseline							
	Lumacaftor 400 mg q12h/ Ivacaftor 250 mg q12h			Placebo			LS mean difference lumacaftor/ivacaftor vs. placebo (95% CI)
	n	Mean Δ baseline ppFEV ₁	SE	n	Mean Δ baseline ppFEV ₁	SE	
Traffic	182	2.16	0.530	184	-0.44	0.524	2.60 (1.18, 4.40)
Transport	187	2.85	0.540	187	-0.15	0.539	3.00 (1.56, 4.44)
Pooled	369	2.49	0.379	371	-0.32	0.376	2.81 (1.80, 3.82)
Harms							
	Lumacaftor 400 mg q12h/ Ivacaftor 250 mg q12h	Placebo	RR (95% CI)	Event rate/100 patients per 24 weeks		RD	
				Lumacaftor 400 mg q12h/ Ivacaftor 250 mg q12h	Placebo		
Subjects with any adverse event							
Pooled	351/369	355/370	0.99 (0.96, 1.02)	95.1	95.9	0.00	
Subjects with any serious adverse event							
Pooled	64/369	106/370	0.61 (0.46, 0.80)	17.3	28.6	-0.11	
Subjects with any treatment related serious event							
Pooled	14/369	8/370	1.75 (0.75, 4.13)	3.8	2.2	0.02	

Abbreviations: SE = Standard error; q12h = every 12 hours; mg= milligrams; LS = least squares; ppFEV₁ = percent predicted FEV₁; CI = confidence interval; RD = risk difference

Source: Compiled during the evaluation/Table B.6.1, p93, Table B.6.4, p103 of the submission and calculated during the evaluation

- 6.18 On the basis of direct evidence presented by the submission, the comparison of lumacaftor/ivacaftor and placebo resulted in:
- Approximately a 2.81% increase in absolute ppFEV₁ over a median duration of follow-up of 24 weeks.
- 6.19 On the basis of direct evidence, the frequency of most adverse effects appears to be comparable between lumacaftor/ivacaftor and placebo; however hepatobiliary serious adverse events occurred in a greater proportion of lumacaftor/ivacaftor patients than placebo patients.

Clinical claim

- 6.20 The submission described lumacaftor/ivacaftor as superior in terms of comparative effectiveness and equivalent in terms of comparative safety over best supportive care. The ESC considered the claim is uncertain for the following reasons:
- The observed treatment effect of 2.81% improvement in ppFEV₁ was considerably smaller than the previously defined MCID of 10% (aztreonam, PSD July 2012). In this context, the ESC agreed that the clinical significance of a 2.81% improvement in ppFEV₁ was highly uncertain, noting that the MCID was met for the ivacaftor monotherapy submission.

- Effectiveness was defined in terms of intermediate outcomes, and the duration of follow-up was short. The evaluation considered that it was uncertain whether the short-term results could be generalised to longer-term efficacy. The PSCR (p4) claimed that evidence of the long term maintenance benefits of lumacaftor/ivacaftor, including effects on ppFEV₁, pulmonary exacerbation rate and BMI were observed in the Progress extension study (a total of 48 weeks treatment). The PSCR (p1) considered that, given the progressive nature of CF and the fact that these benefits occurred on top of subjects' usual CF treatment, the maintenance of treatment effects over this duration is highly clinically relevant. The ESC remained concerned about the short duration of the follow-up, and questioned whether a 2.81% improvement in ppFEV₁ represented a treatment effect which would be sustained over time.
 - In terms of comparative safety, the ESC considered that lumacaftor/ivacaftor appeared to be equivalent to best supportive care on the basis of most outcome measures; however there were a higher proportion of patients that had hepatobiliary serious adverse events in the lumacaftor/ivacaftor arm than in the placebo arm of the clinical trials. This is consistent with the recommendation for liver function tests (ALT, AST and bilirubin) at 1, 3, 6, 9, and 12 months during the first year of treatment, and annually thereafter in the TGA Product Information.
- 6.21 The pre-PBAC response (p1-2) argued that the ppFEV₁ improvement observed for lumacaftor/ivacaftor in the F508del homozygous population should not be compared with the improvement observed for ivacaftor monotherapy in the G551D population; the response argued that the comparison was irrelevant given the differences in the underlying cellular biology and mechanism of action. The response further stated that lumacaftor/ivacaftor addresses the underlying cause of F508del cystic fibrosis and has an impact on lung preservation, prevention of pulmonary exacerbations and improvement in nutritional status.
- 6.22 The pre-PBAC response also argued (p2-3) that the ESC's focus on ppFEV₁ as the primary outcome was too narrow in the context of a disease which affects multiple organ systems and results in a variety of clinical phenotypes across various affected body systems. The response highlighted the fact that statistically significant improvements were observed in terms of pulmonary exacerbations and associated hospitalisations, and treatment with intravenous antibiotics. The pre-PBAC response further argued that there is no empirically agreed definition of MCID for ppFEV₁. The response stated that an important component of treating cystic fibrosis is to maintain stability in lung function, with each 1% reduction in ppFEV₁ increasing the risk of death by 4%. In this context, the response argued that a 2.81% improvement was clinically meaningful. The response also argued that patients treated with lumacaftor/ivacaftor experienced a significant reduction in pulmonary exacerbations, irrespective of their acute change in ppFEV₁.
- 6.23 The PBAC noted the improvement in exacerbations, weight gain, BMI, the hospitalisation rate and antibiotic use associated with treatment with lumacaftor/ivacaftor in the short term but considered that the impact of ivacaftor/lumacaftor on improvements in long-term lung function and survival was uncertain.

- 6.24 The PBAC considered that the claim of equivalent comparative safety was reasonable in the short term but noted the long term safety of lumacaftor/ivacaftor is unknown.

Economic analysis

- 6.25 A summary of the model structure is presented in the table below. The ESC noted that the model presented in the submission was similar in structure to the model for ivacaftor monotherapy.

Table 8: Summary of model structure and rationale

Component	Summary
Time horizon	Life time horizon in the model base case versus 24 weeks in trial (with a further 24 weeks trial data presented as supportive evidence)
Outcomes	QALYs
Methods used to generate results	Patient level microsimulation
Health states	Cox-proportional hazards survival model (Liou et al, 2001) used to apply the effect of 9 risk factors on the baseline hazard of mortality. In lumacaftor/ivacaftor patients ppFEV ₁ , weight-for-age z-score and number of pulmonary exacerbations are based on trial results.
Cycle length	4 weeks

Source: compiled during the evaluation

- 6.26 The effect of intermediate outcomes on survival was estimated using Liou et al. (2001), which was based on historical data. In their previous consideration of ivacaftor monotherapy, the PBAC stated that the use of the Liou et al. data assumed that the ‘effects on survival are causal and additive’ and that this ‘may not be appropriate’ (ivacaftor, July 2013 PSD). The PSCR (p6) argued that the assumption of additive effects is consistent with CF as a multi-system disease. The ESC noted that the Liou study included patients who were alive on 1 January 1993 and for whom follow up data were available through to 31 December 1997 and considered that the conclusions may therefore not be relevant to current clinical practice. In particular, the ESC considered that many of the factors preceding death in the study will no longer be as relevant to the current patient population. Accordingly, the ESC remained concerned about the appropriateness of assuming an additive effect. The pre-PBAC response (p4) countered that Liou and Adler (2015) recently confirmed that the coefficients for mortality predictors, most notably ppFEV₁, weight and pulmonary exacerbations, remained stable from 1993 to 2010. The response further reiterated that Liou et al (2001) found that effects were additive, and asserted that interactions have been fully investigated and incorporated into the model based on the relationships observed in the data.
- 6.27 The ESC noted that while the submission presented a descriptive analysis to make the case for the importance of pulmonary exacerbations, they were included in the model only in terms of contribution to mortality which was modelled based on projected change in FEV₁. Accordingly, the impact of pulmonary exacerbations on health related quality of life was not included in the model.
- 6.28 The ESC also noted that the utility values used in the model were not from either of the pivotal trials (Traffic or Transport), despite the EQ-5D-3L being available, but were derived from a clinician survey. The ESC noted that the utility values were the same as those that were applied to the March 2014 ivacaftor submission.

from 1980 - 2004, and expressed doubt as to whether this historical data accurately reflects the current survival in the Australian CF population.

- 6.33 The impact of the assumptions in the above paragraph is that all lumacaftor/ivacaftor patients will have a survival/QALY gain regardless of the magnitude of the modelled ppFEV₁ increase. While noting the arguments in the PSCR, the ESC remained concerned about the short duration of the follow-up, and questioned whether a 2.81% improvement in ppFEV₁ represented a treatment effect which would be sustained over time.
- 6.34 A summary of the health care resource items used in the economic evaluation is shown in the following table.

Table 10: List of health care resource items and summary of incremental cost

Model Step	Resource use group	BSC costs (\$)	Lumacaftor/ivacaftor + BSC costs (\$)	Incremental cost (\$)	% of total incremental cost
Step 1: 24-week time- horizon	Lumacaftor/ivacaftor	\$ 0.00	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]%
	BSC disease management	\$ 18,697.50	\$ [REDACTED]	-\$ [REDACTED]	- [REDACTED]%
	Lung transplantation	\$ 0.00	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]%
	Adverse event management	\$ 14.87	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]%
	Liver function tests	\$ 0.00	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]%
	Total	\$ 18,712.37	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]%
Step 2: 10-year time horizon	Lumacaftor/ivacaftor	\$ 0.00	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]%
	BSC disease management	\$ 281,926.26	\$ [REDACTED]	-\$ [REDACTED]	- [REDACTED]%
	Lung transplantation	\$ 3,545.43	\$ [REDACTED]	-\$ [REDACTED]	- [REDACTED]%
	Adverse event management	\$ 198.49	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]%
	Liver function tests	\$ 0.00	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]%
	Total	\$ 285,670.18	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]%
Step 3: life-time time horizon (base case)	Lumacaftor/ivacaftor	\$ 0.00	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]%
	BSC disease management	\$ 367,863.85	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]%
	Lung transplantation	\$ 11,891.25	\$ [REDACTED]	-\$ [REDACTED]	- [REDACTED]%
	Adverse event management	\$ 261.98	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]%
	Liver function tests	\$ 0.00	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]%
	Total	\$ 380,017.08	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]%

Source: Table D.5.3, p165 of the submission

- 6.35 The ESC noted that the submission took the cost of BSC health care resources items, other than the management of adverse events, from Van Gool et al (2013); these costs were based on patient age and CF severity. The ESC considered that the costs in Van Gool would already include the cost of managing adverse events, and so the submission's method potentially overestimated the cost of BSC.
- 6.36 A summary of the results of the economic evaluation is shown in the following table.

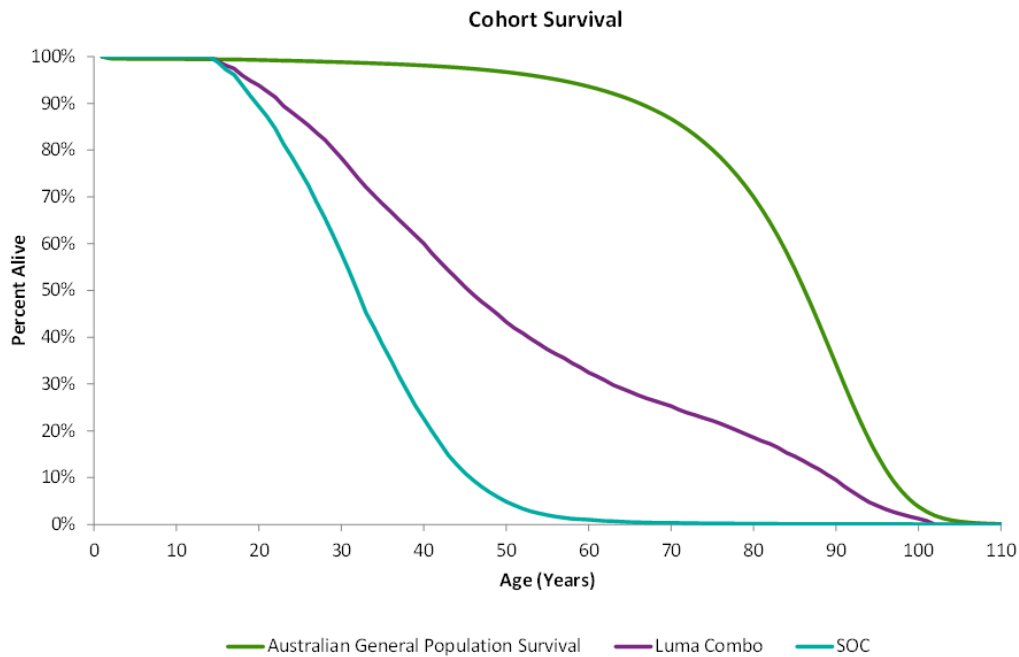
Table 11: Results of the stepped economic evaluation

Step and component	BSC	Lumacaftor/ivacaftor	Increment
Step 1: 24-week time-horizon			
Costs	\$18,712	\$ [REDACTED]	\$ [REDACTED]
QALYs	0.322	0.328	0.007
Incremental cost/extra QALY gained			\$ [REDACTED]
Step 2: 10-year time horizon			
Costs	\$285,670	\$ [REDACTED]	\$ [REDACTED]
QALYs	3.916	5.035	1.119
Incremental cost/extra QALY gained			\$ [REDACTED]
Step 3: life-time time horizon (base case)			
Costs	\$380,017	\$ [REDACTED]	\$ [REDACTED]
QALYs	4.894	9.553	4.659
Incremental cost/extra QALY gained			\$ [REDACTED]

Source: Table D.5.5, p 166 of the submission

- 6.37 The submission presented univariate sensitivity analyses. The sensitivity values presented by the submission ranged from \$105,000/QALY - \$200,000/QALY when differential discounting was applied to more than \$200,000 per QALY when the annual rate of decline in ppFEV₁ in lumacaftor/ivacaftor patients was set to [REDACTED]% of BSC. Additional univariate sensitivity analyses conducted during the evaluation highlighted that the model was also sensitive to the assumption of a [REDACTED]% price reduction at patent expiry (resulting in an ICER of more than \$200,000/QALY) and to the modelled ppFEV₁ decline after 24 weeks in BSC patients (ICER of more than \$200,000/QALY per QALY if no additional decline assumed). The ESC noted the ICER for lumacaftor/ivacaftor should be considered in the context of a much larger patient population and much smaller clinical benefit compared with ivacaftor monotherapy. In this context, the PBAC recommended ivacaftor monotherapy for listing with an ICER of \$105,000/QALY - \$200,000/QALY and only considered this to be acceptable with a 'pay for performance' arrangement together with other risk sharing measures (March 2014 ivacaftor PSD).
- 6.38 Figure 2 below shows the survival predicted by the economic model. The median survival in the BSC arm was 31.92 and in the lumacaftor/ivacaftor arm was 45.48. The median survival in the Irish cohort (which informed the BSC arm of the model) was 39.9 years. The difference in median survival for the BSC group and the Irish cohort is due to the assumed decline in ppFEV₁ in BSC patients.

Figure 2: Cohort survival predicted by the economic model



Source: Figure D.5.1, p167 of the submission

Drug cost/patient/year: \$ [REDACTED]

6.39 The cost per pack of lumacaftor/ivacaftor (28 days treatment) is \$ [REDACTED]. Based on a 15% dose reduction due to hepatic impairment and to account for adherence, the submission assumed 11 packs per patient per year at a cost of \$ [REDACTED]. Treatment is ongoing for the lifetime of the patient.

Estimated PBS usage & financial implications

6.40 This submission was not considered by DUSC. The submission used an epidemiological approach.

Table 12: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Uptake rate	100%	100%	100%	100%	100%
Scripts	[REDACTED] ^a	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated net cost to PBS/RPBS/other government budgets					
Net cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to non-PBS services	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Estimated total net cost					
Net cost to government health budgets	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

^a Assuming 11 scripts per year as estimated by the submission.
Source: Table E.2.7, p174 and Table E.4.2, p 178 of the submission

6.41 By year 5, the estimated number of patients is less than 10,000 and the net cost to the PBS would be more than \$100 million.

- 6.42 The ESC considered that number of patients estimated by the submission as eligible for treatment with lumacaftor/ivacaftor was reasonable (based on the requested listing of patients aged 12 years or older).
- 6.43 There is the potential for off-label use to occur in patients aged less than 12 years old and in patients who have other CF mutations, particularly those who are heterozygous for the F508del mutation. Ivacaftor monotherapy is currently listed for use in cystic fibrosis patients aged 6 years or older, with a G551D or other gating (class III) mutation in the CFTR gene. The ESC noted that clinical trials of this drug have been conducted in children less than 12 years of age.
- 6.44 The PSCR (p6) argued that there is minimal chance of leakage as the PBS listing will specify strict age and genotype eligibility requirements, and these will be subject to authorisation.

Financial Management – Risk Sharing Arrangements

- 6.45 The submission stated that the sponsor is 'open to discussing the details of the requested listing and the final pricing arrangement'. No further detail was provided in the submission, the PSCR or the pre-PBAC response.

7 PBAC Outcome

- 7.1 The PBAC decided not to recommend lumacaftor with ivacaftor for PBS listing based on an unacceptably high and uncertain incremental cost-effectiveness ratio at the requested price, and uncertainty around the impact of lumacaftor/ivacaftor on long-term improvements in lung function and survival.
- 7.2 The PBAC recognised the potential clinical value of lumacaftor/ivacaftor in the treatment of cystic fibrosis in patients aged 12 years or older who are homozygous for the F508deletion mutation (F508del/ F508del).
- 7.3 The PBAC acknowledged the many consumer comments received, both from people living with the condition and on behalf of patients and their carers. The PBAC also acknowledged the correspondence from the Thoracic Society of Australia and New Zealand, and Cystic Fibrosis Australia (and state based equivalents). In addition, representatives of the PBAC met with Cystic Fibrosis Australia prior to the PBAC meeting to discuss the clinical place, benefits and side effects of lumacaftor/ivacaftor for the requested patient population. The Committee recognised the strong support for subsidised access to lumacaftor/ivacaftor.
- 7.4 The PBAC considered best supportive care was the appropriate comparator.
- 7.5 The PBAC considered the argument in the pre-PBAC response comparing the ppFEV₁ results obtained with lumacaftor/ivacaftor in the F508del/F508del population to those for ivacaftor monotherapy in the G551D population is irrelevant for the assessment of clinical significance of lumacaftor/ivacaftor given the differences in the underlying cellular biology and mechanism of action. However, the PBAC considered that while the patient populations differed, the PBAC recommendation for ivacaftor is

a precedent for what constitutes a clinically meaningful improvement in the primary outcome and acceptable cost-effectiveness, in this setting.

- 7.6 In this regard, the PBAC noted that, based on two head-to-head trials comparing lumacaftor/ivacaftor to placebo, lumacaftor/ivacaftor resulted in a 2.81% (95% CI: 1.80, 3.82) increase in absolute ppFEV₁ over a median duration of follow-up of 24 weeks. The PBAC agreed with ESC that it was uncertain whether this observed improvement in ppFEV₁ represented a clinically significant difference, noting that this was considerably smaller than the improvement of 10.58% (95% CI: 8.57, 12.59) demonstrated for ivacaftor monotherapy.
- 7.7 The PBAC considered the pre-PBAC response's argument that focusing on ppFEV₁ results was too narrow in the context of a disease that affects multiple organ systems. The PBAC noted the statistically significant improvement in the number of pulmonary exacerbations (including exacerbations requiring hospitalisation and/or intravenous antibiotics) and weight gain, associated with treatment with lumacaftor/ivacaftor through to week 24. However, the PBAC noted that there was no statistically significant difference in the quality of life measure (CFQ-R). Furthermore, the PBAC agreed with ESC that the extrapolation of short-term results to longer-term efficacy was uncertain.
- 7.8 The PBAC further noted the pre-PBAC response's argument that patients treated with lumacaftor/ivacaftor experienced a significant reduction in pulmonary exacerbations, irrespective of their acute change in ppFEV₁. Given the observed relationship between ppFEV₁ and pulmonary exacerbations, the PBAC considered that it was difficult to interpret the impact of the effect of lumacaftor/ivacaftor on reduction in pulmonary exacerbations independent of its effect on ppFEV₁.
- 7.9 The PBAC noted the ACPM advice on the clinical significance of the small improvement in ppFEV₁ as a primary endpoint, and the validity of putting greater emphasis on secondary endpoints (p6) which stated, "both pivotal studies met the primary endpoint and secondary lung function end points were also met. However, the Quality of Life (QoL) endpoint [CFQ-R] was not met and the BMI endpoint was not met in Study 103. Importantly the exacerbation endpoint was met in both studies. The demonstrated benefit is modest at best, and given the lack of QoL improvement demonstrated, may not be clinically significant in some patients."
- 7.10 The PBAC noted that the frequency of most adverse events appeared to be comparable between lumacaftor/ivacaftor and placebo; however, hepatobiliary serious adverse events occurred in a greater proportion of lumacaftor/ivacaftor patients than in placebo patients. In addition, the PBAC noted that the long-term safety of lumacaftor/ivacaftor is unknown.

Cost-effectiveness of lumacaftor/ivacaftor

- 7.11 The PBAC considered that, at the requested price, the requested listing for lumacaftor/ivacaftor was not sufficiently cost effective to enable PBAC recommendation for PBS listing. Additionally, the PBAC considered that the estimated cost per QALY was likely to be underestimated for the reasons discussed in the following three paragraphs.

- 7.12 The PBAC noted that the model relies on the assumption that the treatment effect is sustained beyond the 24 weeks of the Traffic and Transport trials (and a further 24 weeks from the extension trial, Progress) to the modelled life time horizon. As the PBAC considered that the extrapolation of short-term results in ppFEV₁ to mortality was highly uncertain, the inclusion of this assumption in the model was not considered reasonable. Furthermore, the PBAC considered that the assumption that patients in the treatment group could not decline in ppFEV₁ was implausible.
- 7.13 The PBAC noted that ppFEV₁ drives the frequency of exacerbations in the model. The PBAC considered this appeared inconsistent with the assertion in the pre-PBAC response that the impact of lumacaftor/ivacaftor on exacerbations was independent of its impact on ppFEV₁. Similarly, the PBAC did not accept the additional contribution of pulmonary exacerbations on mortality, independent of effect on FEV₁.
- [REDACTED]
- 7.14 The PBAC agreed with ESC that the base case ICER of more than \$200,000 per QALY was unacceptably high and likely underestimated. The PBAC recalled that it recommended ivacaftor for listing with an ICER of \$105,000/QALY - \$200,000/QALY, in conjunction with risk sharing and pay-for-performance arrangements (Ivacaftor PSD, March 2014). The PBAC considered that, given the more modest clinical benefit, the price of lumacaftor/ivacaftor was too high to result in acceptable cost-effectiveness, even if it was recommended [REDACTED] with Special Pricing Arrangements.
- 7.15 The PBAC noted that the net cost of lumacaftor/ivacaftor to government over the first five years of listing was estimated to be approximately more than \$100 million, with an estimated less than 10,000 patients treated in year 5. The PBAC noted the significant opportunity cost of listing lumacaftor/ivacaftor, particularly in the context of the uncertainty of the long-term improvements in lung function.
- 7.16 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 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.

9 Sponsor's Comment

The sponsor had no comment.