5.08 LUMACAFTOR with IVACAFTOR, Tablet containing lumacaftor 100 mg with ivacaftor 125 mg, Orkambi®, Vertex Pharmaceuticals (Australia) Pty Ltd

1 Purpose of Application

1.1 The submission presented an application for Section 100 (Highly Specialised Drugs Program) listing for lumacaftor 100 mg with ivacaftor 125 mg in a fixed dose combination (lumacaftor/ivacaftor) for the treatment of patients with cystic fibrosis (CF) aged 6–11 years who are homozygous for the F508del mutation in the CF transmembrane conductance regulator (CFTR) gene. The key components of the submission are presented in Table 1.

1.2 This is the first submission for lumacaftor/ivacaftor for this indication in this age group. Lumacaftor 200 mg/ivacaftor 125 mg for the treatment of CF in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene was first considered by the PBAC in March 2016. A minor resubmission was considered in November 2016, and a major resubmission was considered and rejected in July 2017. A subsequent resubmission was lodged in April 2018.

1.3 The submission presented one pivotal trial comparing lumacaftor/ivacaftor with placebo in children 6-11 years, and a cost-utility analysis (CUA) of lumacaftor/ivacaftor + Best Supportive Care (BSC) versus BSC alone for its use in all children 2 and over with an F508*del* mutation in the CFTR gene. In accordance with the TGA registration status of the product and TGA-PBAC parallel process arrangements, consideration of the evidence for this submission was restricted to children 6 and over.

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

Component	Description
Population	CF patients aged 6–11 years who are homozygous for the F508del mutation in the CFTR gene.
Intervention	Two tablets (containing lumacaftor 100 mg/ivacaftor 125 mg) taken orally every 12 hours with total daily dose of 400 mg for lumacaftor and 500 mg for ivacaftor.
Comparator	Best Supportive Care
Outcomes	Primary outcome: $LCI_{2.5}$. Secondary outcomes: ppFEV1, sweat chloride, nutritional status (BMI, BMI-for-age z-score, weight, weight-for-age z-score, height, height-for-age z-score, stature, stature-for-height), $LCI_{5.0}$, pulmonary exacerbation and quality of life (CFQ-R Respiratory Domain Score)
Clinical claim	In CF patients aged 6-11 years who are homozygous for the F508del mutation, lumacaftor/ivacaftor plus BSC is superior in terms of effectiveness compared with BSC alone and non-inferior in terms of safety compared to BSC alone.

Abbreviations: BMI = body mass index; BSC=best supportive care CF=cystic fibrosis; CFQ-R=Cystic Fibrosis Questionnaire-Revised; CFTR=cystic fibrosis transmembrane conductance regulator; FE-1=faecal elastase 1; FEV=forced expiratory volume; IRT=immunoreactive trypsinogen; LCI2.5=lung clearance index at 2.5% of starting concentration; ppFEV1= percent predicted forced expiratory volume in one second; TSQM=Treatment Satisfaction Questionnaire for Medication.
Source: Table 1.1.1, p.30 of the submission.

2 Requested listing

2.1 This submission requested PBS listing for lumacaftor/ivacaftor (Orkambi™) in CF patients aged 6–11 years who are homozygous for the F508del mutation in the CFTR gene (see Table 2).

Table 2: Summary of proposed listing

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
lumacaftor 100 mg/ ivacaftor 125 mg tablets	Pack containing 112 tablets	5	$[redacted]	Orkambi™ Vertex Pharmaceuticals (Australia) Pty Ltd

Category/Program:	Section 100 Highly Specialized Drug Program
PBS indication:	Treatment of cystic fibrosis in patients aged ≥2 years who are homozygous for the F508del mutation in the CFTR gene.
Treatment phase:	Initial
Restriction:	Authority Required
Treatment criteria:	Patients 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.
Clinical criteria:	Treatment of cystic fibrosis in patients who are homozygous for the F508del mutation in the CFTR gene.
Population criteria:	Patients must be aged ≥2 years.
Prescriber criteria:	The authority application must be in writing and must include: (1) a completed authority prescription form; and (2) a completed Cystic Fibrosis Lumacaftor with Ivacaftor Authority Application Supporting Information Form; and (3) a signed patient acknowledgement; or an acknowledgement signed by a parent or authorized guardian; if applicable; and (4) a copy of the pathology report detailing the molecular testing for the patient being homozygous for the F508del mutation on the CFTR gene

Abbreviations: CFTR=Cystic Fibrosis transmembrane conductance regulator; PBS= Pharmaceutical Benefits Scheme
Source: Table 1.4.2, p.58 of the submission.

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

3 Background

Registration status

3.1 **TGA status**: The submission was made under TGA-PBAC Parallel Process. At the time of PBAC consideration, the TGA delegate had indicated an intention to approve for registration, subject to the sponsor committing to 'facilitating the provision of long term efficacy and safety date from use in the Australian Health Care setting'.

3.2 At the time of submission to the PBAC, a TGA application had not been lodged for lumacaftor/ivacaftor in patients aged 2-5 years.

Previous PBAC consideration

3.3 This is the first time the PBAC has considered a submission for lumacaftor/ivacaftor for this age group.

3.4 The PBAC has considered submissions for lumacaftor/ivacaftor for use in patients aged 12 years and older on three separate occasions. The PBAC considered a fourth submission for lumacaftor/ivacaftor for the 12+ age group concurrently with this submission. See public summary document (PSD) for item 7.10 from July 2018.

4 Population and disease

4.1 CF is a rare, genetic, systemic disease caused by a mutation in the CFTR gene that encodes an epithelial chloride channel, the CFTR protein. The failure to regulate chloride transport in the lungs, pancreas, intestinal tract, biliary tract, sweat glands, and reproductive tract results in the multi-system pathology typically exhibited by children with CF early in life. Patients with CF are pancreatic insufficient from an early age. The most common mutation in Australia is F508*del* (which results in deletion of phenylalanine in the CFTR protein), which is present in at least one allele in approximately 90% of CF patients. Approximately 50% of CF patients are homozygous for the F508*del* mutation in Australia.

5 Comparator

5.1 The PBAC accepted best supportive care (BSC) as nominated by the submission, as the comparator. The PBAC previously accepted that BSC is the appropriate comparator for the 12+ population.

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a combined hearing for both lumacaftor with ivacaftor submissions (patients aged 6 – 11 years [item 5.08] and patients aged 12 years and older – [item 7.10]). The presentation focussed predominantly on treatment outcomes in younger patients (aged 6 - 11 years); however, the clinician noted the benefits of treatment with lumacaftor/ivacaftor in both age groups. The clinician stressed the importance of early treatment in CF to prevent or delay lung damage and reduce the rate of decline in lung function; noting that lung function declines over time, particularly beyond the age of 10, and that changes that occur to the lungs between the ages of 5 – 12 can be reversible. The clinician considered that the Lung Clearance Index (LCI) was a useful outcome measure that allows changes to be observed in early lung disease and in response to a question from the PBAC, indicated that a 15% change in LCI was thought to be clinically meaningful. The PBAC noted that the absolute change in LCI observed in Study 109 (10%) was less than 15%.

6.2 In response to a question from the PBAC in relation to the availability of data on the use of lumacaftor/ivacaftor for periods of longer than 24 weeks, the clinician indicated that such data were now available.

6.3 The PBAC noted that a 96 week open label extension study (Study VX15-809-110, also referred to as Study 110) in 6 – 11 year olds is underway, and that preliminary data from that study was presented at the 31st Annual North American Cystic Fibrosis Conference, Indianapolis, Indiana, November 2-4, 2017 (Chilvers M 2017[1], PBAC July 2018 Submission, Section 2, Attachments). According to the information including in the poster, at the time of its preparation, all but one of 239 subjects had completed 72 weeks of study treatment.

6.4 The PBAC noted its ESC had requested further information on the expected completion date of Study 110, but the sponsor did not provide this information in its pre-PBAC response. However, the PBAC noted that the US clinical trials website reports August 2018 as the expected study completion date (https://clinicaltrials.gov/ct2/show/NCT02544451?term=VX15-809-110&rank=1). An August 2018 study completion date is also consistent with the last patient study visit for the studies that preceded Study 110 (and from which patients in Study 110 were drawn) having taken place on 20 September 2016 (CSR Protocol VX14-809-109, 18 January 2017).

6.5 The PBAC further noted that the US clinical trials website reports that the following outcome measures have been included in Study 110.

Primary Outcome Measures:

1. Treatment Cohort: Assess safety and tolerability of long term treatment of lumacaftor in combination with ivacaftor, based on treatment emergent adverse events and changes in clinical laboratory values, vital signs, and spirometry.

Secondary Outcome Measures:

1. Treatment Cohort: Absolute change in Lung Clearance Index 2.5 (LCI2.5) (subjects from Study 109 and the Study 011B LCI Substudy only)
2. Treatment Cohort: Absolute change in sweat chloride
3. Treatment Cohort: Absolute change in body mass index (BMI)
4. Treatment Cohort: Absolute change in Cystic Fibrosis Questionnaire Revised (CFQ-R) respiratory domain score
5. Observational Cohort: Safety, as determined by serious adverse events (SAEs)
6. Treatment Cohort: Absolute change in Lung Clearance Index 5.0 (LCI5.0) (subjects from Study 109 and the Study 011B LCI Substudy only)

[1] Chilvers M-809_110_IA2_NACFC_2017_Poster278_Presented.pdf

7. Treatment Cohort: Absolute change in percent predicted forced expiratory volume in 1 second (ppFEV1)
8. Treatment Cohort: Relative change in ppFEV1
9. Treatment Cohort: Absolute change in body mass index (BMI)-for-age-z-score
10. Treatment Cohort: Absolute change in weight
11. Treatment Cohort: Absolute change in weight-for-age-z-score
12. Treatment Cohort: Absolute change in height
13. Treatment Cohort: Absolute change in height-for-age-z-score
14. Treatment Cohort: Absolute change in Treatment Satisfaction Questionnaire for Medication (TSQM) domains
15. Treatment Cohort: Time-to-first pulmonary exacerbation (subjects from Study 109 only)
16. Treatment Cohort: Event of having at least 1 pulmonary exacerbation (subjects from Study 109 only)
17. Treatment Cohort: Number of pulmonary exacerbations (subjects from Study 109 only)
18. Treatment Cohort: Rate of change in LCI2.5 (subjects from Study 109 and the Study 011B LCI Substudy only)
19. Treatment Cohort: Rate of change in LCI5.0 (subjects from Study 109 and the Study 011B LCI Substudy only).
20. Treatment Cohort: Rate of change in ppFEV1.

6.6 The PBAC noted the sponsor's commitment in the pre-PBAC response to providing the data from Study 110 when finalised.

6.7 The PBAC considered it appropriate for the sponsor to provide further outcome data for ivacaftor/lumacaftor in the 6 – 11 age group for the PBAC's consideration, particularly in the context of a long term treatment for young children which has the potential to cause adverse events. In this context, the PBAC noted that a full report of the planned interim analysis of Study 110 (as referred to in Chilvers, M 2017) should now be available and that data for the full study period should be available in the near future.

Consumer comments

6.8 The PBAC noted and welcomed the input from individuals (3980), health care professionals (45) and organisations (5) via the Consumer Comments facility on the PBS website for both lumacaftor with ivacaftor submissions combined (patients aged 6 – 11 years [item 5.08] and patients aged 12 years and older – [item 7.10]). 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 improvement in quality of life. The comments noted that the very high cost of the drug on the private market puts it out of the financial reach of Australian patients and a number of comments expressed

frustration that lumacaftor/ivacaftor has not yet been recommended for listing, despite a number of submissions being made to the PBAC.

6.9 The PBAC noted the advice received from the Cystic Fibrosis Centre Directors (representing interests from the Cystic Fibrosis Specialist Interest Group of the Thoracic Society of Australia and New Zealand, and Cystic Fibrosis Australia), Cystic Fibrosis Australia and Cystic Fibrosis SA. The PBAC specifically noted the advice that the use of lumacaftor/ivacaftor may halt or slow decline in lung function; reduce hospital stays, IV treatments and hospitalisation costs; and improve nutritional status and quality of life. The advice received from the Cystic Fibrosis Centre Directors also noted that in the experience of Australian CF physicians who have used this drug in trials and on the compassionate Special Access Scheme, patients have experienced a reduction in acute respiratory exacerbations. The advice states that "acute respiratory exacerbations in CF result in worsening of lung function, permanent loss of lung function and decreased survival" and that "any therapy that reduces the rate of acute exacerbations is likely therefore to have a very beneficial effect on the clinical course of patients with CF." The PBAC noted that although this advice was supportive of the evidence provided in the submission, the authors were not able to provide data from Australian patients to substantiate these observations ahead of PBAC consideration.

Clinical trials

6.10 The submission was based on one randomised clinical trial comparing lumacaftor/ivacaftor to placebo, Study 109 (VX15-809-109). In addition, one supplementary supportive open-label, two part study (Study 011) was included.

6.11 The submission excluded one potentially relevant study, Study 110, on the basis that it was currently ongoing and complete data were not yet available. At noted above, the PBAC considered that data from this study would provide important information on the efficacy and safety of lumacaftor/ivacaftor in patients 6 – 11 years.

6.12 Details of the trials presented in the submission are provided in Table 3.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Study 109	A Randomized, Double-blind, Placebo-controlled Multicenter, Parallel group, Phase 3 Study of lumacaftor in combination with ivacaftor in Patients 6 through 11 Years with Treatment-naive Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation	January 2017
	Ratjen F, Hug C, Marigowda M, et al. Efficacy and safety of lumacaftor and ivacaftor in subjects aged 6–11 years with cystic fibrosis homozygous for F508del-CFTR: a randomized, placebo-controlled phase 3 trial.	The Lancet Respiratory Medicine. 2017; 5(7): 557–567
	Brody AS, Nagle SK, Owen CA, et al. Effect of lumacaftor/ivacaftor on total, bronchiectasis, and air trapping computed tomography scores in children with Cystic Fibrosis Homozygous for F508del: Exploratory imaging substudy	North American Cystic Fibrosis Conference, Indianapolis, USA, 2017.
	Nagle SK, Brody AS, Woods J, et al. Feasibility of ultrashort echo time magnetic resonance imaging to evaluate the effect of lumacaftor/ivacaftor therapy in children with cystic fibrosis homozygous for F508del	North American Cystic Fibrosis Conference, Indianapolis, USA, 2017
Study 011	An Open-label, Phase 3 Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Lumacaftor in Combination with Ivacaftor in Patients 6 Through 11 Years of Age With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation	March 2016.
	Chilvers M, Tian S, Marigowda G, et al. An open-label extension (EXT) study of lumacaftor/ivacaftor (LUM/IVA) therapy in subjects aged 6 to 11 years with cystic fibrosis (CF) homozygous for F508del-CFTR.	British Thoracic Society Winter Meeting, United Kingdom, 2017. Thorax. 2017; 72(Suppl 3): A58

Source: Table 2.1.3, p.63-64 of the submission.

6.13 The key features of the direct randomised trial(s) 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
Lumacaftor/ivacaftor vs. placebo						
Study 109	204	R, DB 24 weeks	Low	CF patients aged 6–11 years who are homozygous for the F508del mutation in the CFTR gene	Primary: $LCI_{2.5}$ Secondary:; $ppFEV_1$; nutritional status; $LCI_{5.0}$; sweat chloride,; CFQ-R Respiratory Domain Score; Pulmonary exacerbation TSQM domain score; FEV1; IRT	$ppFEV_1$
Study 011	68	OL 26 weeks	High due to lack of blinding Low for other types of bias	CF patients aged 6–11 years who are homozygous for the F508del mutation in the CFTR gene	Secondary endpoints: sweat chloride ; BMI and BMI for age z score; weight and weight for age z score; height and height for age z score; CFQ-R respiratory domain score; TSQM; ppFEV1	Not used

Abbreviations: DB=double blind; OL=open label; R=randomised.
Source: Compiled during the evaluation. CSR 109 and CSR 011.

6.14 The LCI is a surrogate outcome that measures the number of lung turnovers needed to reduce the marker gas concentration to the pre-defined fraction of the starting concentration. The primary outcome in Study 109 used $LCI_{2.5}$ to demonstrate the number of turnovers to reach the concentration of 2.5% of the marker gas.

6.15 The submission nominated a minimum clinically important difference (MCID) for the primary outcome of $LCI_{2.5}$, and for the secondary outcome of CFQ-R for Study 109.

The proposed MCID for $LCI_{2.5}$ was a change in response of 0.5-1.0 units. The MCID for $LCI_{2.5}$ was based on feedback from the Vertex Advisory Board (4 board members). There is no established, externally validated, MCID for LCI. It is uncertain how the improvement in $LCI_{2.5}$ affects survival. The $LCI_{2.5}$ was not used as a primary outcome in previous submissions and was not used in the economic model in the current submission.

6.16 In the Pre-Sub-Committee Response (PSCR) the sponsor stated that it selected LCI as the primary outcome based on clinical and scientific advice; and noted advice received from the European Medicines Agency Committee for Medicinal Products for Human Use (EMA CHMP) that "The CHMP agrees that LCI can provide a more sensitive outcome measure than FEV_1 in early lung disease such as that present in the majority of patients who are 6 to 11 years of age, thereafter agree with the use of LCI as a measurement of lung function to evaluate the efficacy of LUM/IVA combination therapy in this target population".

6.17 The PBAC agreed with its ESC that the use of the LCI as the primary endpoint in the clinical studies may be reasonable, but noted that there was uncertainty in: the clinical implications of changes observed; the longer-term benefits of these changes; and the relationship of these changes to patient relevant outcomes. The PBAC did not accept the sponsor's apparent assertion that by making these observations it would "*effectively penalise the younger children for the very presence of an additional lung function outcome in their pivotal trial*".

6.18 The PBAC noted that the outcome of $ppFEV_1$, typically used as a key outcome in the management and research of CF, was a secondary outcome in Study 109, and is the only outcome from Study 109 used to estimate the treatment effect in the economic model.

Comparative effectiveness

6.19 The results for the primary efficacy outcome in Study 109 are presented in Table 5. The results of Study 109 showed a statistically significant difference of -1.09 units in $LCI_{2.5}$ in those treated with lumacaftor/ivacaftor compared with placebo. Part B of the supportive study, Study 011, included an LCI sub-study which reported an absolute change in $LCI_{2.5}$ from baseline of -0.97 units in those treated with lumacaftor/ivacaftor compared with placebo.

Table 5: **Absolute change from baseline in $LCI_{2.5}$ at week 24 by MMRM based on FAS in Study 109**

$LCI_{2.5}$ (units)	**Study 109**	
	Lumacaftor 200 mg q12h/ ivacaftor 250 mg q12h (N=103)	**Placebo (N=101)**
Baseline[a]		
Mean (SD)	10.30 (2.36)	10.26 (2.24)
Absolute change through Week 24		
LS Mean (SE)	-1.01 (0.13)	0.08 (0.13)
LS mean difference (95% CI)	**-1.09 (-1.43, -0.75)**	
P value	**<0.0001**	

Abbreviations: CI=confidence interval; FAS=full analysis set; LS=least squares; MMRM=mixed model repeated measures; LCI2.5=lung clearance index 2.5; q12h=every 12 hours; q12h=every 12 hours SD=standard deviation; SE=standard error.
Note: [a] includes all patients without any post-baseline assessments.
Source: Table 2.1.15 p.86 of the submission

6.20 The PBAC noted the sponsor's comments in the pre-PBAC response

"Furthermore, regarding the MCID construct, it may be informative for the PBAC members to contrast the magnitude of the LCI improvement seen with LUM/IVA® treatment in just 24 weeks of the pivotal trial (1.09 unit improvement in 24 weeks) with that reported as CF natural history by Stanojevic, Davis et al, 2017. They report the annual decline in LCI in 2.5 to 6-year old patients to be 0.4 units/year — equating approximately 0.18 unit worsening in 24 weeks. We trust the PBAC can reasonably interpret the clinical meaningfulness of a directional difference in the context of expected natural history"

6.21 The PBAC further noted that in contrast to the results reported by Stanojevic, the mean worsening in LCI in the placebo treated group on study 109 was 0.08 units.

6.22 The PBAC agreed that the directional change in LCI observed over 24 weeks in lumacaftor/ivacaftor in Study 109 was positive but remained uncertain what this change would mean in terms of the overall health of this patient cohort over the longer term.

6.23 The absolute and relative changes in $ppFEV_1$ at week 24 were statistically significant and showed 3% and 3.8% improvements in favour of lumacaftor/ivacaftor respectively (see Table 6).

Table 6: Absolute change from baseline in secondary lung function outcomes ($ppFEV_1$) in Study 109

$ppFEV_1$	**Lumacaftor 200 mg q12h/ ivacaftor 250 mg q12h N=103**	**Placebo (N=101)**
MMRM analysis of absolute change in $ppFEV_1$ from baseline through Week 24 (FAS)		
Baseline[a]		
Mean (SD)	88.8 (13.7)	90.7 (10.8)
Absolute change through Week 24		
LS Mean (SE)	2.5 (0.9)	-0.5 (0.9)
LS mean difference (95% CI)	**3.0 (0.5, 5.5)**	
P value	**0.0195**	
MMRM analysis of relative change in ppFEV1 from baseline through Week 24 (FAS)		
Baseline[a]		
Mean (SD)	1.5 (11.1)	-1.7 (7.8)
Relative change through week 24		
LS Mean (SE)	3.8 (1.2)	0.0 (1.2)
LS mean difference (95% CI)	**3.8 (0.7, 7.0)**	
P value	**0.0174**	

Abbreviations: CI=confidence interval; FAS=full analysis set; LS=least squares; MMRM=mixed model repeated measures; ppFEV1=percent predicted forced expiratory volume in one second; $LCI_{2.5}$=lung clearance index 2.5; q12h=every 12 hours SD=standard deviation; SE=standard error

Note: [a] includes all patients without any post-baseline assessments

Source: Table 2.1.17, p. 91 of the submission

6.24 The results from Study 109 showed no statistically significant difference between lumacaftor/ivacaftor or placebo in either the number of pulmonary exacerbations (PEx) or the proportion of patients having at least one PEx over 24 weeks. The evaluation noted that these results should be interpreted with caution due to the small number of patients with events. Previously (July 2017), the PBAC had been informed by the sponsor that avoidance of PEx was a major clinical benefit of the use of lumacaftor/ivacaftor in patients aged 12 and over with the F508*del* mutation in the CFTR gene. It is feasible that the absence of such an effect in Study 109 is due to a lower baseline risk of PEx in this population due to better baseline lung health, relative to older populations, but this has not been substantiated.

6.25 The absolute change in the CFQ-R domain at week 24 showed no statistically significant difference between lumacaftor/ivacaftor and placebo. The submission noted that there was a within group improvement in CFQ-R domain scores for both treatment groups, but this did not achieve statistical significance (p=0.063). This apparent lack in difference in CFQ-R scores is reflected in a lack of difference in patient reported acceptability of effectiveness, safety, convenience, or overall satisfaction associated with lumacaftor/ivacaftor

6.26 There was a statistically significant reduction in $LCI_{5.0}$ for lumacaftor/ivacaftor compared with placebo of -0.44 week 24.

6.27 The results showed a statistically significant reduction in absolute sweat chloride for lumacaftor/ivacaftor compared with placebo of 20.8 mmol/L at day 15 and 24.9 mmol/L at week 24.

6.28 The impact of lumacaftor/ivacaftor on BMI and BMI for age z scores at week 24 was

not statistically significantly different from placebo. Similarly, the impact of treatment on weight, weight for age Z-scores, height and height for age Z-scores at week 24 was not statistically significantly different from placebo.

6.29 The PSCR and pre-PBAC responses argued that although there is currently no longer-term data available for 6-11 year old patients, the magnitude of the $ppFEV_1$ improvement at week 24 (3.0%) is similar to that observed in the ≥12-year old patients (2.8%); and therefore it is anticipated that efficacy would follow a similar pattern to that observed in the ≥12-year old patients who are homozygous for the F508del mutation. The PSCR further stated that that "the main objective of CF treatment is to minimise the rate of deterioration over time" and that although not directly applicable to patients aged 6-11 years, the reduction in the rate of decline of $ppFEV_1$ observed in patients aged 12+ (42%), 12 – 17 years (45%) and ≥18-year (41%), suggests that "the longer-term impact of Orkambi of slowing the trajectory of FEV_1 over time is consistent across age groups".

6.30 The PBAC considered that overall, the data available for lumacaftor/ivacaftor in the 6-11 age group are supportive of a benefit from treatment, particularly in terms of LCI and ppFEV1, but considered that the impact of lumacaftor/ivacaftor on improvements in long-term lung function and survival was uncertain.

Comparative harms

6.31 A summary of the adverse events for lumacaftor/ivacaftor versus placebo is presented in Table 7. Based on the relative risks estimated during the evaluation (see Table 8), there were no categories of AEs that occurred statistically significantly more frequently with lumacaftor/ivacaftor compared with placebo. With respect to specific events, there was a higher risk of productive cough (RR=2.94 (95%CI 1.22, 7.11)) among patients treated with lumacaftor/ivacaftor compared with placebo, but no difference in the risk of infections and infestations. There was very limited long-term evidence supporting safety of lumacaftor/ivacaftor for treatment of CF in patients aged 6-11 years beyond the 24 weeks reported in Study 109 (Chilvers M 2017, poster).

Table 7: Summary of key adverse events in the trials

Study 109	Lumacaftor 200 mg q12h/ ivacaftor 250 mg q12h N=103	Placebo N=101	RR (95% CI)*
Total number of AEs	573	562	N/A
Patients with any AEs n (%)	98 (95.1)	98 (97.0)	0.98 (0.927, 1.036)
Patients with AEs by maximum severity			N/A
Mild	46 (44.7)	41 (40.6)	0.87 (0.635, 1.202)
Moderate	49 (47.6)	49 (48.5)	0.98 (0.737, 1.304)
Severe	3 (2.9)	8 (7.9)	0.65 (0.111, 3.830)
Life-threatening	0	0	N/A
Missing	0	0	N/A
Patients with AEs leading to treatment discontinuation n (%)	3 (2.9)	2 (2.0)	0.65 (0.111, 3.830)
Patients with AEs leading to treatment interruption n (%)	9 (8.7)	3 (3.0)	0.33 (0.091, 1.172)
Patients with SAEs n (%)	13 (12.6)	11 (10.9)	0.83 (0.390, 1.764)
Patients with related SAEs n (%)	2 (1.9)	3 (3.0)	1.47 (0.251, 8.618)
Patients with AEs leading to death n (%)	0	0	N/A

Abbreviations: AEs=adverse events; MedDRA=Medical Dictionary for Regulatory Activities; N=total sample size; n=number of patients; PT=preferred term; SAEs=serious adverse events; SOC=system organ class.
Notes: *Calculated values. RR not provided by the submission.
Source: Table 2.1.24 p 105 of the submission

6.32 On the basis of the direct evidence from Study 109 presented by the submission the frequency of adverse events being reported was comparable between lumacaftor/ivacaftor and placebo groups. The most common AE in patients who received lumacaftor/ivacaftor were cough (44.7% compared to 46.5%), infective pulmonary exacerbation (19.4%), productive cough (17.5% compared to 5.9%), nasal congestion (16.5% compared to 7.9), oropharyngeal pain (14.6% compared to 9.9%), pyrexia (14.6% compared to 19.8%), upper respiratory tract infection (12.6% compared to 9.9%) and headache (12.6 compared to 8.9). A total of 5 (2.5%) patients had SAEs considered related (related or possibly related, as determined by the investigator) to the study drug (3 (3.0%) in placebo and 2 (1.9%) in lumacaftor/ivacaftor group).

Benefits/harms

6.33 A summary of the comparative benefits and harms for lumacaftor/ivacaftor versus placebo in children 6-11 years of age is presented in Table 8.

Table 8: Summary of comparative benefits and harms for lumacaftor/ivacaftor and placebo

Benefits							
Absolute change from baseline in $LCI_{2.5}$ at 24 weeks							
Study 109	**Lumacaftor/ivacaftor**			**Placebo**			**Mean difference*: Lumacaftor/ivacaftor vs. placebo (95% CI)**
	N	**Mean Δ baseline $LCI_{2.5}$**	**SD**	**N**	**Mean Δ baseline $LCI_{2.5}$**	**SD**	
	103	10.30	2.36	101	10.26	2.24	-1.09 (-1.43, -0.75)
Absolute change from baseline in $ppFEV_1$ at 24 weeks							
Study 109	**Lumacaftor/ivacaftor**			**Placebo**			**Mean difference*: Lumacaftor/ivacaftor vs. placebo (95% CI)**
	N	**Mean Δ baseline $ppFEV_1$**	**SD**	**N**	**Mean Δ baseline $ppFEV_1$**	**SD**	
	103	88.8	13.7	101	90.7	10.8	3.0 (0.5, 5.5)

Harms						
	Lumacaftor/ivacaftor n/N	**Placebo n/N**	**RR (95% CI)**	**Event rate/100 patients***		**RD[a] (95% CI)**
				Lumacaftor/ivacaftor	**Placebo**	
Total number of patients with AEs						
Study 109	98 /103	98/101	0.98 (0.927, 1.036)	95.1	97.0	-1.88 (-7.19, 3.42)
Total number of SAEs						
Study 109	13/103	11/101	0.83 (0.390, 1.764)	12.6	10.9	1.73 (-7.01, 10.56)
AEs leading to treatment discontinuation n (%)						
Study 109	3/103	2/101	1.47 (0.251, 8.618)	2.91	1.98	0.93 (-3.30, 5.17)
AEs related to study drug						
Study 109	2/103	3/101	0.65 (0.111, 3.830)	1.94	2.97	-1.03 (-5.28, 3.22)

*Maximum duration of follow-up: Study 109 = 4 weeks

Abbreviations: AE = adverse event; CI = confidence interval; FEV_1 = predicted expiratory volume in one second; HR = hazard ratio; LCI = lung clearance index; PBO = placebo pp = percent predicted; RD = risk difference; RR = risk ratio; SAE = serious adverse event; SD = standard deviation;

Note: [a] calculated by the Commentary

Source: Table 2.1.15 p.86, Table 2.1.17, p. 91, Table 2.1.24 p 105 of the submission

6.34 On the basis of direct evidence from Study 109 presented by the submission, the comparison of lumacaftor/ivacaftor and placebo resulted in:

- An improvement of 1.09 units in lung clearance index after 24 weeks of treatment.
- An increase in the lung capacity (as measured by the percent predicted forced expiratory volume) of 3% after 24 weeks of treatment.
- No difference in the likelihood of harm over 24 weeks of treatment.

Clinical claim

6.35 The submission described lumacaftor/ivacaftor as superior in terms of effectiveness compared with BSC and non-inferior in terms of safety compared to BSC. The submission stated that lumacaftor/ivacaftor improved key CF treatment outcomes that are associated with prolongation of life expectancy; $LCI_{2.5}$ and $ppFEV_1$. The submission stated that the safety and efficacy profile of lumacaftor/ivacaftor in CF aged 6-11 years is comparable to that observed in other age groups (i.e. CF patients aged ≥12 years).

6.36 The PBAC considered that the therapeutic conclusion presented in the submission was not adequately supported over the longer term for the following reasons:

- While the data showed statistically significant differences in the $LCI_{2.5}$ and ppFEV1 based on 24 weeks of data, the long-term implications of those differences are unknown. This is particularly relevant in light of the data from the PROGRESS study that demonstrated that the modest ppFEV1 increase in lumacaftor/ivacaftor treated patients was not maintained in the longer term, with the improvement from baseline not being statistically significant at 120 weeks (PROGRESS).
- There is no established minimum clinically important change in LCI and it is uncertain how improvements in $LCI_{2.5}$ may contribute to patient relevant outcomes that lead to improvements in survival or quality of life.
- The claim lumacaftor/ivacaftor is non-inferior to BSC in terms of comparative safety is not adequately supported, particularly in the absence of long-term data.

6.37 Thus, while there is evidence of a difference in efficacy in favour of lumacaftor/ivacaftor compared with placebo in the short-term, the data presented by the submission does not inform that comparison over the long-term, which is particularly relevant in the context of a life-long condition and treatment.

Economic analysis

6.38 The submission presented a cost utility analysis economic evaluation, based on direct randomised trials and implementing a modelled evaluation, comparing lumacaftor/ivacaftor with BSC. The economic evaluation presented included all patients aged 2 years and older with the F508*del* mutation (2 – 5, 6-11 and 12+).

6.39 While the submission presented a model which incorporated patients 2 years and over, the clinical data presented were for those aged 6-11 only. The economic model was evaluated for patients aged 6-11 years, and for those 6 and older, or 12 and older by using the 'patient filter' functionality provided in the Excel workbook. Aspects of the model specification or outputs which were specific to the 2-5 age group were not evaluated.

6.40 As in previous lumacaftor/ivacaftor submissions (March 2016, November 2016 and July 2017) and lumacaftor monotherapy submissions (July 2013 submission and March 2014 resubmission) the model was based on the Cox-proportional hazard (CPH) survival model described in Liou et al (2001). The model structure is the same as that previously evaluated by the PBAC. There are some changes to the model inputs (costs, treatment effects) to capture the paediatric population aged ≥ 6 years and the application of the submissions' initially proposed annual financial cap of $[redacted] per patient.

6.41 Given that the submission presented the same model structure and inputs (for

children aged 12 and over) as considered previously by the PBAC, the key model inputs varied by the PBAC in its respecification of the base case at its July 2017 meeting (para 6.57, July 2017 PSD), and how they have been addressed in the current submission, are summarised in Table 9.

Table 9: Summary of variations made by PBAC to previous model and how they have been considered in this submission

Component	Previous PBAC Preferred Scenarios	Current Approach
Ivacaftor/Lumacaftor cap and price adjustments	Removal of the 5% statutory price reduction and [redacted]% generic price reduction. Removal of the proposed cap.	Price reductions were reinstated. A utilisation cap resulting in a price of $[redacted] per patient per year is utilised. Removal of price reductions and the cap is tested in sensitivity analyses (Table 13).
Sustained clinical effect	Assumed that the decline in $ppFEV_1$ for lumacaftor/ivacaftor post 24 weeks was 100% of that seen in BSC.	The post 24 week decline in $ppFEV_1$ for lumacaftor/ivacaftor was set at [redacted]% of that of BSC. Varied to [redacted]%, [redacted]% and [redacted]% in sensitivity analyses (Table 13).
Cost reductions due to hospitalisations	Assumed that only 75% of CF hospitalisations are due to PEx and therefore eligible for cost-reductions.	Assumed that all CF hospitalisations are due to PEx, and that there was a reduction of 61% of hospitalisations. Varied to 0% reduction in sensitivity analyses (Table 13). The submission also assumed no reduction in PEx among children 6-11.

Abbreviations: BSC=best supportive care; CF=cystic fibrosis; PEx=pulmonary exacerbations; $ppFEV_1$ =percent predicted forced expiratory volume in one second.
Source: Compiled during the evaluation from the July 2017 PBAC Public Summary Document, Lumacaftor/Ivacaftor.

6.42 The model initially provided with the July 2018 submission adjusted the rate of decline in the lumacaftor/ivacaftor treatment group to [redacted]% of that in the BSC group; reinstates the 5% and [redacted]% price reductions; and assumes that all CF hospitalisations are due to PEx, and that there was a reduction of 61% of hospitalisations.

6.43 The key components of the economic evaluation are presented in Table 10.

Table 10: Summary of model structure and rationale

Component	Summary
Time horizon	Lifetime in the modelled base case. Patients aged ≥ 12 years: 24 weeks in TRAFFIC/TRANSPORT and PROGRESS (extension to 96 weeks). Patients aged 6-11 years: 24 weeks in Study 109.
Outcomes	Quality-adjusted life years.
Methods used to generate results	Individual patient microsimulation. Liou CPH model used to apply the effect of nine risk factors on the baseline hazard of mortality.
Health states	As a microsimulation, changes are recorded in the underlying risk factors (as above) for each patient. Utility values are applied to 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	Modelled survival using Liou CPH model. Treatment effects were based on Study 109 ($ppFEV_1$ for patients aged 6-11 years) and TRAFFIC/TRANSPORT (weight-for-age z-score). Changes in treatment effect and patient characteristics over time from PROGRESS (decline in $ppFEV_1$ post 24 weeks) and change in weight-for-age z-score. Baseline hazard function from Cystic Fibrosis Registry of Ireland 2013.

Abbreviations: CPH = Cox Proportional Hazards; FEV_1 =forced expiratory volume in one second; pp = percent predicted;
Source: Table 3.1.1, p.151 of the submission

6.44 The key drivers of the model are in Table 11.

Table 11: Key drivers of the model

Description	Method/Value	Impact
Proposed Financial Cap	Annual Cap of $[redacted] applied for lumacaftor/ivacaftor drug cost	High, favours lumacaftor/ivacaftor
Modelled change in $ppFEV_1$ in lumacaftor/ivacaftor patients.	Treatment effect continued beyond 24 week trial period for life time. Updated data from extension trial PROGRESS were not included in the model.	High, favours lumacaftor/ivacaftor
Modelled change in $ppFEV_1$ in BSC patients.	Annual decline in $ppFEV_1$ after the first 24 weeks	High, favours lumacaftor/ivacaftor
Assumption of price reduction at patent expiry.	[redacted]% price reduction at end of patent life	High, favours lumacaftor/ivacaftor
Assumption of reduction in PE-related hospitalisation costs for lumacaftor/ivacaftor.	61% reduction in PE-related hospitalisation costs; estimated by multiplying hospitalisation costs associated with BSC by 0.61.	Moderate, favours lumacaftor/ivacaftor
Extrapolation of survival	Liou et al (2001), extrapolation of effect of intermediate outcomes on survival.	High, favours lumacaftor/ivacaftor

Abbreviations: BSC = best supportive care; PE = pulmonary exacerbation; $ppFEV_1$= per cent predicted forced expiratory volume in one second.
Source: compiled during the evaluation.

6.45 Results from the economic evaluation with a respecified base case (to reflect use only in those 6 and over) are presented in Table 12. These results show that the cost per QALY gained for patients 6 and over was estimated to be $105,000 - $200,000. Restricting the analysis to those aged 6-11 years reduced the ICER to $105,000 - $200,000 per QALY, while it increased to $105,000 - $200,000 per QALY when restricting the analysis to those 12 and over. These ICERs include the future price reductions (described in 6.49 below).

Table 12: Results of the economic evaluation

Step and component	Lumacaftor/ivacaftor	Best supportive care	Increment
Patients aged 6 years and older, revised base case with cap			
Costs	$	$469,441	$
QALYs	8.30	6.08	2.21
Incremental cost/extra QALY gained			$
Patients aged 6-11 years, scenario with cap			
Costs	$	$611,930	$
QALYs	13.89	10.70	3.19
Incremental cost/extra QALY gained			$
Patients aged 6-11 years, scenario without cap			
Costs	$	$611,930	$
QALY	13.89	10.70	3.19
Incremental cost/extra QALY gained			$
Patients aged 12 years and older, scenario with cap			
Costs	$	$437,044	$
QALYs	6.91	4.94	1.97
Incremental cost/extra QALY gained			$
Patients aged 12 years and older, scenario without cap			
Costs	$	$437,044	$
QALY	6.91	4.94	1.97
Incremental cost/extra QALY gained			$

Abbreviations: QALY=quality adjusted life year.
Note: Base case ICER from the submission of patients aged 2 years and older is $ per QALY gained with incremental cost of $ and incremental QALY of 2.29.
Source: Compiled during the evaluation setting the patient filter to patients aged 6 years and older. Excel spreadsheet "Orkambi 2+ cost effectiveness model March 2018 FINAL', sheet 'Results'.

The redacted table shows ICERs in the range of $105,000/QALY – more than $200,000/QALY.

6.46 The model initially provided with the July 2018 submission incorporated a decline in $ppFEV_1$ in lumacaftor/ivacaftor patients beyond the 24 weeks trial period to life time at a rate of % of BSC decline (declines of % and % were tested in the sensitivity analysis; Table 13). This decline was informed by the longer term $ppFEV_1$ data from the extension trial PROGRESS, which showed that patients on lumacaftor/ivacaftor had a decline in FEV that was 58% that of matched control group in follow up to 96 weeks. This differs from the July 2017 resubmission of lumacaftor/ivacaftor in patients aged 12 years and older as previously it was assumed that there was no decline in $ppFEV_1$ post 24 weeks in the lumacaftor/ivacaftor treated patients. Sensitivity analysis setting the decline to 100% of BSC (see Table 14) resulted in an ICER of more than $200,000.

6.47 Of the three treatment effect characteristics captured by the Liou CPH model, the only input value specific to patients aged 6 to 11 taken from Study 109 was for $ppFEV_1$. The model assumed that patients aged 6 to 11 years would have the same changes in weight-for-age z-score (which was available from Study 109, where there was no significant difference) as the patients aged 12 years and older from PROGRESS. Using the weight-for-age z-score from Study 109 (same for lumacaftor/ivacaftor and BSC) had minimal impact on the ICER.

6.48 The submission assumed that there would be no difference in PEx for patients aged 6 to 11 years between those treated with BSC and lumacaftor/ivacaftor. This was appropriate given that Study 109 did not find any statistically significant differences in the number of PEx. However, the PBAC noted that the submission applied a 61.5% reduction to hospitalisation-specific disease management costs for the lumacaftor/ivacaftor arm of the model for all age groups controlling for $ppFEV_1$, which was not justified by the evidence presented in the submission.

6.49 The submission applied a 5% statutory price reduction after 5 years and a [redacted]% reduction in cost following generic entry after loss of exclusivity date (7.94 years) to this cap. The PBAC has previously considered that the application of such price reductions is inappropriate (paragraph 6.42, July 2017 PSD). The ESC noted that removing these price reductions in the model resulted in an increase to the base case ICER (for patients aged 6 years and over) from $105,000/QALY - $200,000/QALY to more than $200,000/QALY. Further, the ESC noted that with tezacaftor/ivacaftor on the horizon (recently approved overseas for patients aged 12 years and older and currently under consideration by the TGA) use of lumacaftor with ivacaftor post-loss of exclusivity may be displaced by this other combination.

6.50 The sensitivity analyses conducted during the evaluation for patients aged 6 years and older which resulted in a variation in the ICER of more than [redacted]% are presented in Table 13 (and in the tornado diagram at Figure 1). These show that the largest single impact on the ICER was due to the application of the proposed financial cap and associated price reductions (removal of the cap resulting in an ICER of more than $200,000 per QALY).

Table 13: Results of sensitivity analyses, patients aged ≥ 6 years (change of 10% or more).

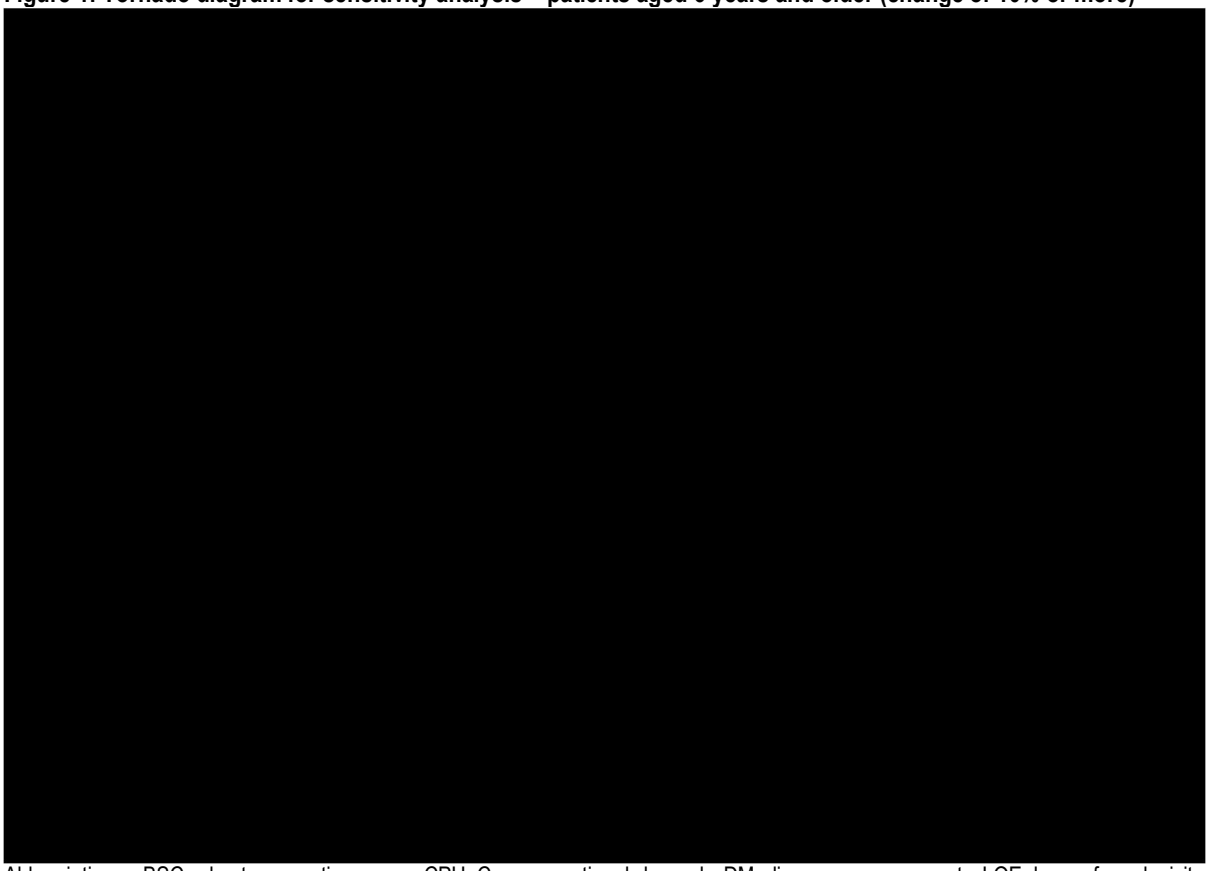
Analysis description	Incremental cost ($)	Incremental effect (QALYs)	ICER (cost per additional QALY gained)
Base case for 6 years and older	$[redacted]	2.21	$[redacted]
Costs/prices			
No financial cap, use effective price	$[redacted]	2.21	$[redacted]
No reduction in price due to LOE and no F1 statutory price reduction	$[redacted]	2.21	$[redacted]
No financial cap or price reduction due to LOE or F1 statutory price reduction	$[redacted]	2.21	$[redacted]
Cost of cystic fibrosis disease management in lumacaftor/ivacaftor arm same as BSC (set 61.5% to 0% reduction)	$[redacted]	2.21	$[redacted]
Effects			
Set annual decline in $ppFEV_1$ in lumacaftor/ivacaftor treated patients to [redacted]% of BSC	$[redacted]	4.69	$[redacted]
Set annual decline in $ppFEV_1$ in lumacaftor/ivacaftor treated patients to [redacted]% of BSC	$[redacted]	3.35	$[redacted]
Set annual decline in $ppFEV_1$ in lumacaftor/ivacaftor treated patients to [redacted]% of BSC	$[redacted]	1.37	$[redacted]
Set annual decline in $ppFEV_1$ in lumacaftor/ivacaftor treated patients to [redacted]% of BSC	$[redacted]	0.73	$[redacted]

Abbreviation: BSC=best supportive care; FEV_1=forced expiratory volume in one second; LOE=loss of exclusivity

Source: Compiled during the evaluation setting the patient filter to patients aged 6 years and older Excel spreadsheet "Orkambi 2+ cost effectiveness model March 2018 FINAL', sheet 'Results'.

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

Figure 1: Tornado diagram for sensitivity analysis – patients aged 6 years and older (change of 10% or more)



Abbreviations: BSC= best supportive care; CPH=Cox proportional hazard; DM=disease management; LOE=loss of exclusivity; PE=pulmonary exacerbation; ppFEV$_1$= percent predicted forced expiratory volume in one second;
Note: Only scenarios with a greater than 10% change in the base ICER were reported.
Source: Compiled during the evaluation setting the patient filter to patients aged 6 years and older Excel spreadsheet "Orkambi 2+ cost effectiveness model March 2018 FINAL', sheet 'Results'.

6.51 An additional multivariate sensitivity analysis was conducted for patients aged 6 years and older to remove the reduction in hospitalisations due to PE, remove the future price reductions (LOE and F1), and assume parallel FEV$_1$ decline (100% of BSC) in the both arms. This resulted in an ICER of more than $200,000 (see Table 14).

Table 14: Results of updated sensitivity analyses, patients aged ≥ 6 years

Analysis description (patients aged 6 years and older)	Incremental cost ($)	Incremental effect (QALYs)	ICER (cost per additional QALY gained)
Base case for 6 years and older	$	2.21	$
Univariate sensitivity analysis			
Remove the future price reductions (LOE and no F1 statutory price reduction)	$	2.21	$
Remove the reduction in hospitalisations due to PE so cost of cystic fibrosis disease management same as BSC (set 61.5% to 0% reduction)	$	2.21	$
Set annual decline in FEV_1 in lumacaftor/ivacaftor treated patients to 100% of BSC	$	0.73	$
Multivariate sensitivity analysis			
Remove the reduction in hospitalisations due to PE, remove the future price reductions (LOE and F1), and assume parallel FEV1 decline (100% of BSC) in the 2 arms.	$	0.73	$

Abbreviation: BSC=best supportive care; FEV_1=forced expiratory volume in one second; LOE=loss of exclusivity

6.52 The pre-PBAC response revised the overall Financial Cap offer (covering the 2 – 5, 6 - 11 and 12+ age groups) to more than $100 million (circa 61.3% rebate) from the more than $100 million offered in the July 2018 submission, to achieve an effective price per treated patient of $ per year.

6.53 The pre-PBAC response also revised the rate of decline for the on-treatment group in the economic model to 42%. These changes resulted in revised ICERs of $105,000/QALY - $200,000/QALY (see Table 15) for the 2+ population, $105,000/QALY - $200,000/QALY for the 6+ population, and $105,000/QALY - $200,000/QALY for the 12+ population.

Table 15: Estimated ICER at effective price of $ per patient per year and with rate of decline 42% of BSC

Patient cohort (years)	ICER
≥ 2	$
≥ 6	$
≥ 12	$

Source: pre-PBAC response – lumacaftor with ivacaftor patients 12 years and older (p.3) and compiled during the evaluation

Drug cost/patient/year: $

6.54 The pre-PBAC response offers a total expenditure cap which it states will deliver a cost per patient of $ per year vis-à-vis a list price of $18,750 per 28 days treatment (approx $244,000 per year).

Estimated PBS usage & financial implications

6.55 The sponsors pre-PBAC revised estimates for patients 2+ and older are presented in Table 16.

Table 16: Submission's pre-PBAC estimated use and financial implications, patients aged 2 years and older

	Source	Year 1	Year 2	Year 3	Year 4	Average/ Total
Treated patients	Section 4 spreadsheet, Cost to Govt PBS, row 5	[redacted]	[redacted]	[redacted]	[redacted]	Average: [redacted]
Proposed Financial Cap	Suggested distribution	$[redacted]	$[redacted]	$[redacted]	$[redacted]	Total: $[redacted]

Source: Table 3 of pre-PBAC response, item 7.10 July 2018

The redacted table shows that the total estimated number of patients over 4 years was less than 10,000 and the net cost to the PBS would be more than $100 million.

6.56 The PBAC considered the submission's estimates for the 6-11 age group to be too high for the following reasons as documented in the ESC advice:

- The estimate of the prevalent pool of 6 – 11 year olds is higher than would be expected based on the estimate of 40 incident patients homozygous for the F508 del mutation each year. On the basis of this incidence figure, it would be expected that the prevalent pool of 6 – 11 year olds would be closer to 240 (ie 6 x 40).
- The submission assumed that patients could only discontinue therapy in the first year. This is based on the pooled discontinuation rates from TRAFFIC and TRANSPORT (6.8% applied to patients aged 6 years and older). 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).

  In addition, a reasonable assumption is that discontinuing patients will discontinue treatment throughout the year, so that on average each patient receives the equivalent of half of a year's supply in the year in which they discontinue treatment.

  Note: The final PROGRESS study report indicates "Other" was the most frequent reason for treatment discontinuation (36.1% of overall subjects), and the vast majority of these discontinuations were because subjects transitioned from study drug to the commercially available supply of drug (PROGRESS study report Version 1.0, 25 October 2016, pp 77). The PBAC does not propose that the discontinuations reported as resulting from patients moving to commercially available drug be taken account for in adjusting the submission's estimates.
- The submission assumed that patients who become eligible for treatment each year receive a full year of treatment. A more reasonable assumption is that initiating patients will commence treatment throughout the year, so that

on average each patient receives the equivalent of half of a year's supply in the year in which they commence treatment.

6.57 The PBAC noted the revised financial impact of listing lumacaftor/ivacaftor in the 6+ population (ie 6-11 and 12+) taking into account these issues as reported in Table 17.

Table 17: Estimated use and financial implications, patients aged 6 years and older

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients treated*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gross cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
With rebate applied					
With [redacted]% rebate ($[redacted] per patient per year)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

* This number includes and adjustment to all for patients initiating and discontinuing treatment throughout the year (i.e. the patient number is expressed as the number treated for a full year equivalents)
Source: Compiled by the secretariat based on submission section 4 spreadsheet with adjustments to remove patients <12 years, to allow discontinuations in year 2 in line with outcomes of PROGRESS study, and with initiating patients in year 3 onwards receiving the equivalent of half of a year's supply in the year in which they commence treatment

The redacted table shows that the total estimated number of patients over 5 years was less than 10,000 and the net cost to the PBS would be more than $100 million.

6.58 The PBAC noted that the sponsor [redacted]. In its pre-PBAC Response, the sponsor reiterated its willingness to be [redacted] (see Table 16).

6.59 The PBAC considered this approach to be associated with a significant risk [redacted]

Managed Access Program

6.60 The PBAC considered that, in the event it decides to recommend the listing of ivacaftor/lumacaftor be extended to include the 6 – 11 age group, it would likely also recommend a Managed Access Program (MAP) of the type described in the PSD for item 7.10 from July 2018.

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

7 PBAC Outcome

7.1 The PBAC deferred making a recommendation to list ivacaftor/lumacaftor on the PBS for patients aged 6–11 years who are homozygous for the F508*del* mutation in the CFTR gene to enable the TGA to finalise its negotiations with the sponsor with respect to the provision of long term efficacy and safety data from use in the Australian Health Care setting.

7.2 The PBAC was reassured by the data from the 24 week randomised, placebo controlled study, Study 109, which showed a similar improvement in ppFEV1 in the 6 – 11 year age cohort as that observed in the 12+ year cohort, despite the group having less potential to improve ppFEV1 than older patient cohorts.

7.3 The PBAC agreed with the rationale for commencing treatments that slow the progression of damage early in the course of a disease. However the PBAC considered the evidence that ivacaftor/lumacaftor is a disease modifying treatment that prevents declines in lung function in patients with Cystic Fibrosis in the long term and improves survival is not yet available.

7.4 The PBAC considered it appropriate for the sponsor to provide further outcome data for ivacaftor/lumacaftor in the 6 – 11 age group for the PBAC's consideration, particularly in the context of a long term treatment for young children which has the potential to cause adverse events. The PBAC noted that a full report of the planned interim analysis of Study 110 (as referred to in Chilvers M, 2017) should now be available and that data for the full study period should be available in the near future.

Outcome:
Deferred

Addendum to the July 2018 PBAC Minutes:

5.08 LUMACAFTOR with IVACAFTOR, Tablet containing lumacaftor 100 mg with ivacaftor 125 mg, Orkambi®, Vertex Pharmaceuticals (Australia) Pty Ltd

8 Background

8.1 At its July 2018 meeting, the PBAC deferred making a recommendation to list lumcaftor/ivacaftor on the PBS for patients with Cystic Fibrosis (CF) aged 6–11 years who are homozygous for the F508*del* mutation in the CF transmembrane conductance regulator (CFTR) gene to enable the Therapeutic Goods Administration (TGA) to finalise its negotiations with the sponsor with respect to the provision of long term efficacy and safety data from use in the Australian Health Care setting.

TGA Status

8.2 Subsequent to the July 2018 meeting, on 10 August 2018, the TGA delegate approved lumacaftor/ivacaftor for registration for use in children aged 6 – 11 years with the following conditions:

- For the purpose of collecting post-market data, [Vertex] should encourage (where feasible) prescribers to notify the Australian CF registry when patients commence treatment with ORKAMBI so that this is entered as a descriptive factor.
- [Vertex is] required to provide the TGA with evidence of the long term efficacy and safety of ORKAMBI when initiated in patients aged 6-11 years in the form of an ongoing post market observational study. The data should include data from both Australian and International CF registries. It should include the impact of ORKAMBI on FEV_1, rate of decline in FEV_1, exacerbations, BMI, diabetes, time to lung transplant, mortality and if possible time off work/school, as well as safety. It should include a comparison of patients not treated with ORKAMBI, preferably controlled for age. It should also include data about safety. Reports should be provided every 5 years for the next 20 years.
- [Vertex] should include details of this post-market study in an updated Australian Specific Annex (ASA) to the EU Risk Management Plan (RMP) and submit it to the TGA for review within three months of the date of this approval letter.

8.3 Following the resolution of the TGA registration, the PBAC was requested by the Minister's delegate to reconsider the listing of lumacaftor/ivacaftor for the treatment of patients with cystic fibrosis (CF) aged 6–11 years.

Estimated PBS usage and financial implications

8.4 The estimated financial impact of extending the listing to include the 6 – 11 year age group was estimated in July 2018 as follows:

Table 18: Estimated use and financial implications, patients aged 6 years and older at $ [redacted] per patient per year

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients treated*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gross cost to PBS/RPBS	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]
With rebate applied					
With [redacted]% rebate ($[redacted] per patient per year)	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]
Cost for 12+ group with [redacted]% rebate applied	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]
Additional cost for 6 – 11 year group	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]

Source: Table 17, PBAC PSD item 5.08 July 2018 & Table 17, PBAC PSD item 7.10 July 2018

The redacted table shows that the total estimated number of patients over 5 years was less than 10,000 and the net cost to the PBS would be more than $100 million.

Managed Access Program and risk share arrangements

8.5 In July 2018, the PBAC considered that, in the event it decides to recommend the listing of ivacaftor/lumacaftor be extended to include the 6 – 11 age group, it would likely also recommend a Managed Access Program (MAP) of the type described in the PSD for item 7.10 (paragraph 6.60 above)

8.6 In July 2018, the PBAC considered that a MAP for lumacaftor/ivacaftor would allow patients in the 12 years and older age group 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 (paragraphs 6.73 – 6.79 of the July 2018 PBAC PSD, item 7.10).

8.7 Under such an MAP, subsidy could be paid at the sponsor's asking price of $[redacted] per patient per year for a period of two and a half years to allow the sponsor to provide further data to satisfy the PBAC that the differences in the rates of decline in lung function ($ppFEV_1$) and pulmonary exacerbations observed in the PROGRESS study are sustained over a longer time period of at least 4 years in real clinical practice.

8.8 If, by the end of the two and a half year initial period of the MAP, the sponsor's assumptions on rate of decline have not been substantiated or have only been partially substantiated, through a submission to the PBAC and the PBAC affirming the cost-effectiveness of the medicine, the PBAC considered that the price paid for lumacaftor/ivacaftor should reduce to a level consistent with the evidence provided.

If that were the case, the minimum price paid in the second half of the MAP would be $[redacted] per patient per year consistent with the assumption that patients treated with lumacaftor/ivacaftor maintain an advantage over untreated patients after 96 weeks, but that treated patients decline at a similar rate to untreated patients. Indicative costs of including patients aged 6 – 11 years in a MAP consistent with that recommended for patients aged 12 years and older are presented in Table 19.

Table 19: Indicative cost to Commonwealth of listing lumacaftor/ivacaftor for patients aged 6 years and over

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
MAP conditions met	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
MAP conditions not met	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

8.9 In July 2018, the PBAC also noted that the sponsor plans to bring forward new treatments for patients who are homozygous for the f508del mutation in the CFTR gene, with tezacaftor with ivacaftor currently undergoing regulatory review and a triple therapy combination treatment in clinical trials. The PBAC recognised that this might limit the availability of longer term data for lumacaftor with ivacaftor but considered that the MAP could allow the PBAC to be provided with longer term data for patients treated continuously with lumacaftor with ivacaftor, as well as treatment with tezacaftor with ivacaftor or triple therapy, or through consecutive periods of treatment with more than one of these regimens.

8.10 At that time the PBAC also considered that it would be appropriate for the Minister to enter into a deed with the sponsor to specify the annual patient cost, overall financial caps and terms of the MAP.

9 PBAC Outcome

9.1 The PBAC recommended, out of session, the listing of lumacaftor with ivacaftor for patients with CF aged 6–11 years who are homozygous for the F508*del* mutation in the CFTR gene on the basis that it should be available only under special arrangements under section 100 (Highly Specialised Drugs Program) and only in the circumstances: for the treatment of patients with CF aged 6 - 11 years who are homozygous for the F508del mutation in the CFTR gene. The PBAC recommended the special arrangements and circumstances described Section 10 below.

9.2 The PBAC is satisfied that lumacaftor with ivacaftor provides, for some patients, a significant improvement in efficacy over best supportive care.

9.3 Consistent with its recommendation for lumacaftor/ivacaftor in patients with CF aged 12 years and older, the PBAC recommendation for listing in patients aged 6 - 11

years was based on, among other matters, its assessment that the cost-effectiveness of lumacaftor/ivacaftor would be acceptable if the following measures were implemented to contain risks associated with the cost-effectiveness and overall cost of the drug to the PBS.

- A Managed Access Program as described in paragraphs 8.5 – 8.10 above;
- A Special Pricing Arrangement to give effect to the offered price of $[redacted] per patient per year; and
- Caps on [redacted] in line with the estimates in Table 19 above.

9.4 In addition, the PBAC recalled that at its July meeting it considered it appropriate for the sponsor to provide further outcome data for ivacaftor/lumacaftor in the 6 – 11 age group for the PBAC's consideration, particularly in the context of a long term treatment for young children which has the potential to cause adverse events. On that basis, the PBAC also recommended that:

- Vertex provide PBAC with an interim report of the post-market study it is undertaking for the TGA, at the same time as it submits to data to the PBAC to satisfy the MAP (on or before the first quarter of the third year of listing); and
- the interim and final results from study 110 (96 weeks open use in 6 - 11 year olds) be submitted to the PBAC within 1 month of the reports being finalised unless one or both reports has already been finalised, in which case the relevant report must be provided to the PBAC within one month of the commencement of subsidy.

9.5 The PBAC recognised the potential clinical value of lumacaftor/ivacaftor in the treatment of cystic fibrosis in patients aged 6 – 11 years who are homozygous for the F508del mutation and recognised the strong support for subsidised access to this medicine and acknowledged the many consumer comments and the correspondence from the Cystic Fibrosis Centre Directors, Cystic Fibrosis Australia and Cystic Fibrosis SA relating to this submission.

9.6 The PBAC did not consider that lumacaftor/ivacaftor should be treated as interchangeable with any other drugs.

9.7 The PBAC advised that lumacaftor/ivacaftor is not suitable for prescribing by nurse practitioners.

9.8 The PBAC recommended that the Early Supply Rule should not apply.

Outcome:
Recommended

10 Recommended listing

Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
lumacaftor 100 mg/ ivacaftor 125 mg tablets	Pack containing 112 tablets	5	Orkambi™ Vertex Pharmaceuticals (Australia) Pty Ltd

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
PBS Indication:	Cystic Fibrosis
Treatment phase:	Initial
Restriction:	☒Authority Required - In Writing
Treatment criteria:	Must be treated by a specialist respiratory physician with expertise in cystic fibrosis, OR Must be treated in consultation with a specialist respiratory physician with expertise in cystic fibrosis if attendance is not possible due to geographic isolation; AND Must be treated in a centre with expertise in cystic fibrosis, OR Must be treated in consultation with a centre with expertise in cystic fibrosis if attendance is not possible due to geographic isolation.
Clinical criteria:	Patient must be homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene; AND The treatment must be given concomitantly with standard therapy for this condition.
Population criteria:	Patient must be aged between 6 and 11 years inclusive.
Prescriber Instructions:	The patient must be registered in the Australian Cystic Fibrosis Database Registry. 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. The authority application must be in writing and must include: (1) a completed authority prescription form; and (2) a completed Cystic Fibrosis Lumacaftor with Ivacaftor Authority Application Supporting Information Form; and and (3) a copy of the pathology report detailing the molecular testing for the patient being homozygous for the F508del mutation on the CFTR gene; and (4) the result of a FEV_1 measurement performed within a month prior to the date of application. Note: FEV_1, must be measured in an accredited pulmonary function laboratory, with documented no acute infective exacerbation at the time FEV_1 is measured; and (5) evidence that the patient has either chronic sinopulmonary disease or gastrointestinal and nutritional abnormalities; and (6) a copy of a current medication history; and (7) height and weight measurements at the time of application; and (8) a baseline measurement of the number of days of CF-related hospitalisation (including hospital-in-the home) in the previous 12 months.

Administrative Advice:	Special pricing arrangements apply No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised. 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). 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 Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
PBS Indication:	Cystic Fibrosis
Treatment phase:	Continuing
Restriction:	☒Authority Required - In Writing
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 aged between 6 and 11 years inclusive.
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. The authority application must be in writing and must include: (1) a completed authority prescription form; and (2) a completed Cystic Fibrosis Lumacaftor with Ivacaftor Authority Continuing Application Supporting Information Form; and (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 (4) a copy of a current medication history; and (5) height and weight measurements at the time of application; and

	(6) the number of days of CF-related hospitalisation (including hospital-in-the home) in the previous 6 months.
Administrative Advice:	Special pricing arrangements apply No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised. 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). 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 Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001

11 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.

12 Sponsor's Comment

The sponsor had no comment.