

## **6.03 LUMACAFTOR WITH IVACAFTOR**

**Sachet containing granules, lumacaftor 150 mg with ivacaftor 188 mg;**

**Sachet containing granules, lumacaftor 75 mg with ivacaftor 94 mg;**

**Sachet containing granules, lumacaftor 100 mg with ivacaftor 125 mg,**

**Orkambi<sup>®</sup>,**

**VERTEX PHARMACEUTICALS (AUSTRALIA) PTY LTD**

### **1 Purpose of submission**

- 1.1 The Category 2 submission requested an extension to the current listing of lumacaftor/ivacaftor for the treatment of cystic fibrosis (CF) patients homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (herein referred to as the F/F population) to include patients aged 1 to less than 2 years. The submission included a request to list an additional strength of the granules for use in the proposed population (lumacaftor 75 mg/ivacaftor 94 mg granules), in addition to those currently available on the PBS. Lumacaftor/ivacaftor is currently listed for patients aged 2 years and older.

Listing was requested on the basis of a modelled cost-utility analysis comparing lumacaftor/ivacaftor + best supportive care (BSC) with BSC. The components of the overall clinical claim addressed by the submission are summarised in

1.2 Table 1.

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

Component	Description
Population	CF patients aged 1 to less than 2 years who are homozygous for the <i>F508del</i> mutation in the <i>CFTR</i> gene
Intervention	For CF patients 1 to less than 2 years weighing 7 kg to <9 kg: one sachet containing 75 mg of LUM and 94 mg of IVA twice daily, approximately 12 hours apart. For CF patients 1 to less than 2 years weighing 9 kg to <14 kg: one sachet containing 100 mg of LUM and 125 mg of IVA twice daily, approximately 12 hours apart. For CF patients 1 to less than 2 years weighing ≥14 kg: one sachet containing 150 mg of LUM and 188 mg of IVA twice daily, approximately 12 hours apart.
Comparator	BSC
Outcomes	Absolute change from baseline in sweat chloride Absolute change from baseline in growth parameters (BMI, BMI-for-age z-score, weight, weight-for-age z-score, length, length-for-age z-score, weight-for-length z-score) Pulmonary exacerbation/hospitalisation measures Absolute change in: FE-1; IRT; lipase; amylase; faecal calprotectin Change from baseline in microbiology cultures
Clinical claim	LUM/IVA plus BSC is superior in terms of effectiveness compared with BSC alone. LUM/IVA plus BSC is comparable in terms of safety to BSC alone.

Source: Table 1.1.1, p25 of the submission.

BMI = body mass index; BSC = best supportive care; CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; FE-1 = faecal elastase 1; IRT = immunoreactive trypsinogen; IVA = ivacaftor; LUM = lumacaftor.

## 2 Background

### **Registration status**

- 2.1 The TGA approval for lumacaftor/ivacaftor was extended on 16 May 2023 to include patients aged 1 year and older for the treatment of cystic fibrosis who are homozygous for the F508del mutation in the CFTR gene.
- 2.2 The TGA Delegate's Overview was provided in the submission and the minutes of the Advisory Committee on Medicines (ACM) meeting became available during the evaluation. The ACM advised that the overall benefit-risk was positive for lumacaftor/ivacaftor in the 1–2-year age group. In the absence of efficacy data, the pharmacodynamic data was considered a suitable surrogate for efficacy. The ACM noted the positive effects on sweat chloride (SwCl), pancreatic function, pulmonary exacerbations and no negative effects on growth parameters.

### **Previous PBAC consideration**

- 2.3 The PBAC has previously recommended a number of submissions to extend the age restriction for CFTR modulators as summarised in Table 2.

**Table 2: First PBAC recommendation for CFTR modulators in CF**

	Lumacaftor/ivacaftor	Ivacaftor	Elexacaftor/tezacaftor/ivacaftor
Current PBS listing	CF homozygous for the F508del mutation in the CFTR gene.	CF with G551D mutation in the CFTR gene on at least one allele  CF with other gating (class III) mutation in the CFTR gene on at least one allele	CF with at least one F508del mutation in the CFTR gene
First recommended by PBAC	Aged ≥ 12 years: July 2018 Aged 6 to 11 years: July 2018 Aged 2 to 5 years: July 2019 Aged 1 to < 2 years: current submission	Aged ≥ 6 years: November 2013 Aged 2 to 5 years: January 2017 Aged 1 to < 2 years: March 2019	Aged ≥ 12 years: July 2021 Aged 6 to 11 years: November 2022

Source: constructed during evaluation

CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme

2.4 The submission for lumacaftor/ivacaftor for patients aged 2 to 5 years was recommended by the PBAC in July 2019. In making that recommendation, the PBAC noted the supporting evidence was limited but acknowledged the difficulties in obtaining efficacy data from paediatric patients. Overall, the PBAC concluded that the claim of superior efficacy over BSC in patients aged 2 to 5 years was biologically plausible (paragraph 7.1, lumacaftor/ivacaftor Public Summary Document (PSD), July 2019 PBAC meeting).

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

### 3 Requested listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
LUMACAFITOR/IVACAFITOR Lumacaftor 75 mg/ivacaftor 94 mg granules, 56 sachets	1	Pack containing 56 sachets	5	Published (public): \$17,812.50	Orkambi®, VX
LUMACAFITOR/IVACAFITOR Lumacaftor 100 mg/ivacaftor 125 mg granules, 56 sachets	1	Pack containing 56 sachets	5	Published (private): \$17,860.32 Effective (public): \$■■■■	
LUMACAFITOR/IVACAFITOR Lumacaftor 150 mg/ivacaftor 188 mg granules, 56 sachets	1	Pack containing 56 sachets	5	Effective (private): \$■■■■ <sup>a</sup>	
<b>Category / Program:</b> Section 100					
<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/>					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – non-immediate/delayed assessment by Services Australia					
<b>Condition:</b> cystic fibrosis - homozygous for the F508del mutation in the CFTR gene (CFTR) gene					
<b>Indication:</b> cystic fibrosis - homozygous for the F508del mutation in the CFTR gene (CFTR) gene (CFTR) gene					
<b>Treatment Phase:</b> Initial treatment					
<b>Clinical criteria:</b>					
Patient must be homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene					

<b>AND</b>
<b>Clinical criteria:</b>
The treatment must be given concomitantly with standard therapy for this condition.
<b>Treatment criteria:</b>
Must be treated in a centre with expertise in cystic fibrosis or in consultation with a centre with expertise in cystic fibrosis if attendance is not possible due to geographic isolation
<b>AND</b>
Must be treated by a specialist respiratory physician with expertise in cystic fibrosis or in consultation with a specialist respiratory physician with expertise in cystic fibrosis if attendance is not possible due to geographic isolation
<b>Population criteria:</b>
Patient must be 1 year of age or older
<b>Prescribing Instructions:</b> This pharmaceutical benefit is not PBS-subsidised for this condition in a patient who is currently receiving one of the strong CYP3A4 inducers outlined in the Product Information.
<b>Administrative Advice:</b> For the purposes of this restriction, PBS-subsidised 'CFTR modulator' means ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor and elexacaftor/tezacaftor/ivacaftor. The authority application must be in writing and must include: (1) a completed authority prescription; and (2) a completed Cystic Fibrosis Authority Application Supporting Information Form; (3) details of the pathology report substantiating the patient being homozygous for the F508del mutation on the CFTR gene - quote each of the: (i) name of the pathology report provider, (ii) date of pathology report, (iii) unique identifying number/code that links the pathology result to the individual patient; and (4) current CYP3A4 inhibitors, CYP3A4 inducers and IV antibiotics.

Source: Table 1.4.2, pp46-47 of the submission.

CFTR = cystic fibrosis transmembrane conductance regulator; IV = intravenous; PBS = Pharmaceutical Benefits Scheme.

<sup>a</sup> calculated during the evaluation.

- 3.1 The proposed PBS listing is consistent with the current listing for lumacaftor/ivacaftor sachets and the draft Product Information.
- 3.2 The submission proposed a special pricing arrangement with the published and effective prices being the same as for the current listings for lumacaftor/ivacaftor sachets.

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

## 4 Population and disease

- 4.1 CF is a rare, genetic, systemic disease caused by mutations in the CFTR gene which ultimately leads to defective transport of chloride and other ions. Patients with CF are subject to a progressive loss of lung function, significant excess morbidity and reduced quality of life (QoL), pancreatic insufficiency and gastrointestinal malabsorption, frequent pulmonary exacerbations (PEx) and early death.
- 4.2 The submission stated that the proposed clinical algorithm for the F/F population aged 1 to less than 2 years was the same as that currently applied in clinical practice for patients aged 2 years and older treated with lumacaftor/ivacaftor granules and tablets.

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

## 5 Comparator

- 5.1 The submission nominated BSC as the main comparator. The submission stated that there are no existing therapies on the PBS that would be substituted for by lumacaftor/ivacaftor.
- 5.2 The choice of comparator was consistent with previous submissions in older populations in which the PBAC accepted BSC as the appropriate comparator for lumacaftor/ivacaftor (paragraph 5.1, lumacaftor/ivacaftor PSD, July 2018 PBAC meeting; paragraph 5.1 and paragraph 7.3, lumacaftor/ivacaftor PSD, July 2019 PBAC meeting). However, the submission did not consider that the requested PBS listing represents an earlier start to therapy (potentially from 1-year of age) as compared with the current PBS listing for lumacaftor/ivacaftor (potentially from 2-years of age). Additionally, the submission did not consider that once patients in the F/F population reach 6 years of age, they will be eligible for elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA).
- 5.3 The ESC considered the nominated comparator was generally reasonable, noting that the intervention most likely to be replaced was BSC from 1 to 2 years of age, followed by lumacaftor/ivacaftor from 2 years of age.

*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 discussed the natural history of the disease and stated the importance of commencing therapy with CFTR modulators early to prevent structural lung damage. The clinician described the benefits of treatment on lung function and quality of life. The clinician further described the benefit of CFTR modulators on the nutritional status of children and the associated weight gain. The PBAC considered that the hearing was informative.

### **Consumer comments**

- 6.2 The PBAC noted and welcomed the input from individuals (68), and organisations (1) via the Consumer Comments facility on the PBS website. The comments, primarily from carers of children with CF, described a range of benefits of treatment with lumacaftor with ivacaftor including reduced long-term lung damage due to a reduced likelihood of contracting bacterial infections, reduced antibiotic use and hospitalisations and improved gastrointestinal symptoms. The comments also highlighted that listing lumacaftor with ivacaftor on the PBS for this age group would improve current access and equity issues.
- 6.3 The PBAC noted the advice received from the National Paediatric Medicines Forum (NPMF) which strongly supported the extension of the lumacaftor with ivacaftor listing to children aged 1 to 2 years, stating that it would help slow the progression of CF and

that it was a safe and well tolerated treatment.

### **Clinical study**

6.4 There were no head-to-head randomised trials available comparing lumacaftor/ivacaftor plus BSC with BSC for the requested ages. The submission was based on one 24-week single arm study evaluating the safety and efficacy of lumacaftor/ivacaftor granules, Study 122 (Part A (N=14); Part B (N=46)).

6.5 Details of the study presented in the submission are provided in Table 3.

**Table 3: Study and associated reports presented in the submission<sup>a</sup>**

<b>Study ID</b>	<b>Protocol title/Publication title</b>	<b>Publication citation</b>
Study 809-122 (NCT03601637)	A Phase 3, Open-Label Study of Lumacaftor/Ivacaftor in Children 1 to Less Than 2 Years of Age with Cystic Fibrosis Homozygous for <i>F508del-CFTR</i>  Rayment, J.H., Asfour, F., Rosenfeld, M., Higgins, M., Liu, L., Mascia, M., Paz-Diaz, H., Tian, S., Zahigian, R. and McColley, S.A., 2022. A phase 3, open-label study of lumacaftor/ivacaftor in children 1 to less than 2 years of age with cystic fibrosis homozygous for F508del-CFTR.	Clinical Study Report, Protocol VX16-809-122  <i>Am J Respir Crit Care Med.</i> 2022 Nov 15;206(10):1239-1247

Source: Table 2.2.1 p52 of the submission

<sup>a</sup> Study 809 – 124 (Long-term Safety of Lumacaftor/Ivacaftor in Subjects with Cystic Fibrosis Who Are Homozygous for F508del and 12 to <24 Months of Age at Treatment Initiation) was mentioned in the submission and a protocol was attached, however no results were available.

6.6 The key features of Study 122 are summarised in Table 4.

Table 4: Key features of the included evidence

	N	Design/duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>Lumacaftor/ivacaftor + BSC</b>						
Study 122	Part A (N=14) Part B (N=46)	OL, MC, 2-part study  Part A: 15 days, dose based on patient weight - 7 to < 10 kg: LUM 75 mg, IVA 94 mg q12h - 10 to < 14 kg: LUM 100 mg, IVA 125 mg q12h - ≥ 14 kg: LUM 150 mg, IVA 188 mg q12h	High <sup>b</sup>	Aged 1 to less than 2 years with CF homozygous for the F508del mutation.	<ul style="list-style-type: none"> <li>Primary: PK.</li> <li>Secondary: safety, tolerability, PK parameters of the metabolites of LUM and IVA.</li> </ul>	No
		Part B: 24 weeks, dose based on patient weight - 7 to < 9 <sup>a</sup> kg: LUM 75 mg, IVA 94 mg q12h - 9 <sup>a</sup> to < 14 kg: LUM 100 mg, IVA 125 mg q12h - ≥ 14 kg: LUM 150 mg, IVA 188 mg q12h			<ul style="list-style-type: none"> <li>Primary: safety and tolerability.</li> <li>Secondary: absolute change from baseline in SwCl at week 24.</li> <li>Additional PD outcomes: Absolute change in SwCl from Week 24 to Week 26. Absolute change from baseline at week 24 in: BMI, BMI-for-age z-score, weight, weight-for-age z-score, length, length-for-age z-score, weight for length z-score, FE-1; IRT, faecal calprotectin, microbiology cultures, LCI, PEx and CF related hospitalisation. Acceptability/palatability of LUM/IVA granules at Day 1</li> </ul>	The only outcome from Study 122 used in the model was weight for age-z score

Source: Table 2.4.7 pp63-64, Table 2.4.8 p65, Table 2.4.9 p67 of the submission, p3 Attachment 8 of the submission  
 BMI = body mass index; CF = cystic fibrosis; FE-1 = faecal elastase-1; IRT = immunoreactive trypsin; IVA = ivacaftor; LCI = lung clearance index; LUM = lumacaftor; MC = multi-centre; OL = open label; PD = pharmacodynamics; PEx = pulmonary exacerbations; PK = pharmacokinetics; q12h = every 12 hours; SwCl = sweat chloride.

<sup>a</sup> During Part B, a review of safety and PK data in Part A and a subset of patients in Part B was completed and incorporated into the popPK models. The updated popPK models supported a decrease in the upper weight bound for the LUM75/IVA94 dose and the lower weight bound for the LUM100/IVA125 dose from 10 kg to 9 kg.

<sup>b</sup> Assessed by the evaluation using the Cochrane Collaboration's tool for assessing risk of bias, to ensure consistency with lumacaftor/ivacaftor submission for the F/F population aged 2 to 5 years.

#### 6.7 Study 122 was a 2-part study:

- Part A was a dose finding study with 3 doses. The objectives were to evaluate the pharmacokinetics (PK) and safety of lumacaftor/ivacaftor. Participants received 15 days of weight-based treatment.
- Part B was a dose confirmation study. The objectives were to evaluate the PK, pharmacodynamics (PD) and safety of lumacaftor/ivacaftor. Participants received 24 weeks of weight-based treatment. The PK and PD of multiple doses of

lumacaftor/ivacaftor over 24 weeks of dosing were evaluated, and a 2-week washout period was included in order to evaluate the off-drug PD response.

- 6.8 The results of Study 122 were vulnerable to confounders and uncertainty due to its open-label nature, absence of a comparator, small sample size and short duration of treatment.

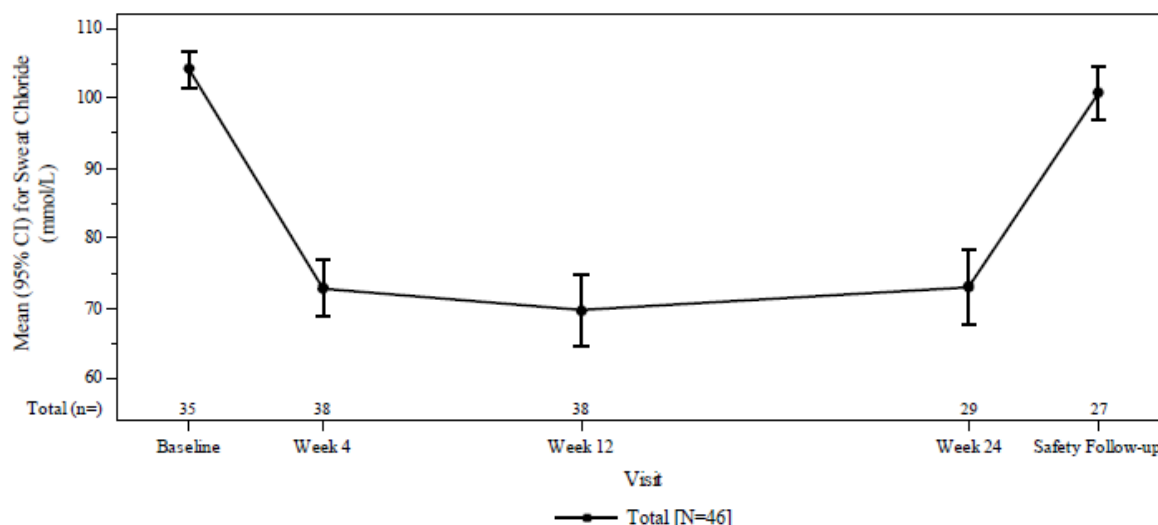
### **Comparative effectiveness**

- 6.9 PK assessment: The lumacaftor and ivacaftor trough concentrations in Parts A and B suggest steady state was achieved prior to Day 15. The lumacaftor and ivacaftor metabolite trough concentrations at steady state and time to achieve steady-state plasma concentrations in subjects 1 to less than 2 years of age with CF were similar to those in subjects 2 to 11 years of age. The TGA Delegate's overview remarked that the number of subjects and PK sampling timepoints appear to be adequate to characterise the PK in this population.
- 6.10 The PBAC has previously considered percent predicted forced expiratory volume in 1 second (ppFEV<sub>1</sub>) as the outcome of interest in CF patients aged ≥ 2 years. The submission noted the difficulty in conducting spirometry in the 1 to less than 2 years cohort. Further, the submission noted the limited interpretability of this outcome in young children with CF, as ppFEV<sub>1</sub> is not a sensitive measure of early structural and functional changes in peripheral airways of young children with CF who are more likely to have normal ppFEV<sub>1</sub> values than older children. Given the absence of ppFEV<sub>1</sub> data for Study 122, it was not possible to provide a comparison based on that outcome, despite it being a key driver of the economic model used to assess the cost-effectiveness of lumacaftor/ivacaftor relative to BSC.
- 6.11 In the absence of ppFEV<sub>1</sub> in this patient cohort, the submission presented a number of PD outcomes as a measure of efficacy. Study 122 demonstrated an overall reduction in SwCl from baseline at Week 24, with levels returning close to baseline after the 2 week washout period (see Figure 1). The mean absolute change from baseline for SwCl at Week 24 was -29.1 mmol/L. This represents a SwCl reduction of 27.9%. The submission did not provide a minimal clinically important difference (MCID) for this outcome. The National Health Service (NHS) of England considers a 30% reduction in SwCl, or SwCl falling below 60 mmol/L, as indicating a response to ivacaftor treatment.<sup>1</sup> The PBAC has previously considered a reduction in SwCl as evidence of biological activity (paragraph 6.22, ivacaftor PSD, March 2019 PBAC meeting) for CFTR modulators in the treatment of patients with CF. In the absence of ppFEV<sub>1</sub> results, the PBAC has considered the comparative improvements in SwCl in the 1 to 2 years cohort, in relation to older age cohorts, as an uncertain but plausible measure of effectiveness (paragraph 6.22, ivacaftor PSD, March 2019 PBAC meeting).

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<sup>1</sup> NHS England, 2015, Clinical Commissioning Policy: Ivacaftor for Cystic Fibrosis (named mutations)

Figure 1: Mean (95% CI) for sweat chloride (mmol/L) at each visit, FAS, Part B



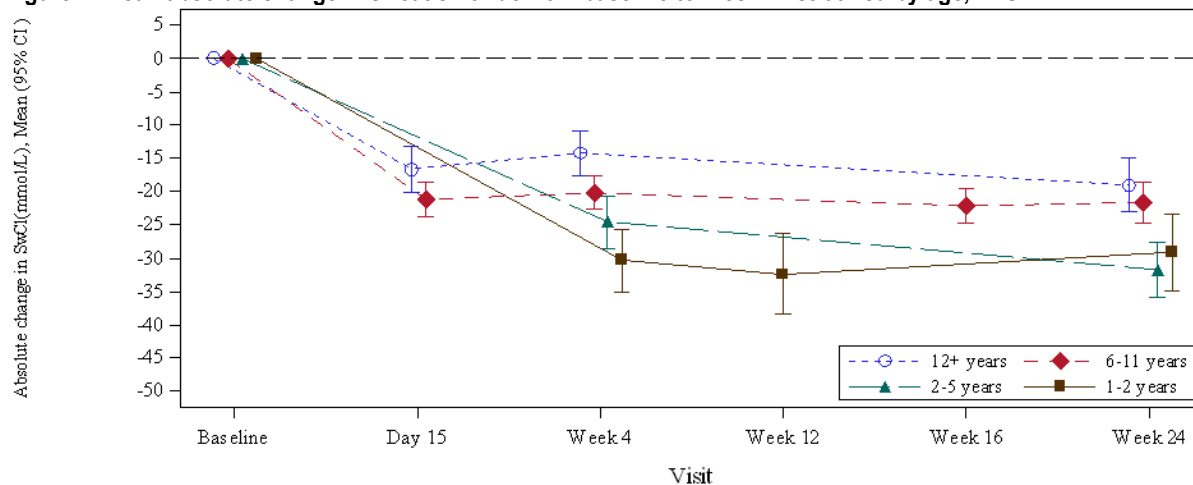
Source: 2.5.1 p70 of the submission  
 CI = confidence interval; FAS = full analysis set.

- 6.12 Improvements were also observed in markers of pancreatic function and inflammation (FE-1, IRT, faecal calprotectin) over the 24-week treatment period. All growth parameters remained stable over time.
- 6.13 The benefits of treatment with lumacaftor/ivacaftor for each of the PD outcomes should be interpreted with caution due to the small sample size of the study (N = 46), short duration of follow up and the lack of a comparable control group.
- 6.14 The submission presented a comparison of SwCl response to 24-week CFTR treatment across Study 122, Study 115 (2 to 5 years), Study 109 (6 to 11 years) and Study 106 (tezacaftor/ivacaftor aged  $\geq 12$  years<sup>2</sup>) in the F/F population (see Figure 2). The submission provided a qualitative interpretation that change in SwCl at Week 24 in Study 122 was comparable with the studies in older patients. The submission noted that patients aged 6 years and older experienced rapid and sustained reductions in SwCl, along with a clinically meaningful change in lung function. On the basis of the comparable rapid and sustained reduction in SwCl seen in Study 122, the submission claimed that it was both plausible and reasonable to anticipate that lumacaftor/ivacaftor would have a positive impact on lung function in younger patients. The submission did not present any other comparative PK or PD data for patients aged 2 years and older.

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<sup>2</sup> SwCl was not collected in the  $\geq 12$  years lumacaftor/ivacaftor trial

Figure 2: Mean absolute change in sweat chloride from baseline to Week 24 stratified by age, FAS<sup>a</sup>



	Number of subjects				
1-2 years (809-122)	35		32	33	24
2-5 years (809-115)	56		45		49
6-11 years (809-109)	102	87	90		90
12+ years (809-106)	45	38	35		32

Source: Figure 2.7.1, p92 of the submission

CI = Confidence Interval; FAS = full analysis set; SwCl = sweat chloride.

Note:

Full Analysis set includes all enrolled or randomised subjects who are exposed to any amount of study drug. The Full Analysis set is defined the same across all studies.

CF patients with F/F genotype aged 1-2 years participated in study 809-122; patients aged 2-5 years participated in study 809-115; patients aged 6-11 years participated in study 809-109; patients aged 12+ years participated in study 809-106. All treatment dosage regimens are pooled from all studies.

Baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) prior to the initiation date of treatment. The baseline is defined the same for all studies.

The values of SwCl at each visit are based on the averaged measurements from left and right arms. This is calculated the same across all studies.

<sup>a</sup> Note that the results presented in Figure 2 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for Studies 809-106, 809-109, 809-115 and 809-122. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.15 The ESC noted the data from Study 116 presented in the Pre-Sub-Committee Response (PSCR) supported sustained reduction in SwCl over 96 weeks but further noted that this study was in children aged 2 to 5 years of age.

### Comparative harms

6.16 A summary of the adverse events (AEs) for lumacaftor/ivacaftor in Study 122 is presented in Table 5.

6.17 Of the 14 patients enrolled in Part A, 12 (85.7%) experienced an AE. No patients experienced a serious AE. Treatment was discontinued in one (7.1%) patient who experienced a rash. The most commonly reported AEs were rhinorrhoea (35.7%), cough (28.6%), rash (21.4%) and influenza (14.3%).

6.18 Of the 46 patients enrolled in Part B, 44 (95.7%) experienced an AE. Five (10.9%) patients experienced a serious AE, while two (4.3%) patients experienced a severe AE.

For comparison, in Study 115 (F/F population aged 2 to 5 years of age), 98.3% of patients experienced an AE, of which 6.7% were a SAE. Treatment in Part B of Study 122 was discontinued in one (2.2%) patient who experienced increase in alanine aminotransferase (ALT) and aspartate transaminase (AST). Treatment was interrupted in two (4.3%) patients, one of whom experienced dyspnoea and the other who had a serious distal intestinal obstruction syndrome which was assessed by the investigator to be related to study drug and treatment.

**Table 5: Overview of AEs in Study 122 Part A and Part B, Safety Set**

	<b>Part A Total N = 14 n (%)</b>	<b>Part B Total N = 46 n (%)</b>
Number of AEs	24	197
Any AEs	12 (85.7)	44 (95.7)
AEs by maximum severity		
Mild	8 (57.1)	24 (52.2)
Moderate	4 (28.6)	18 (39.1)
Severe	0	2 (4.3)
Life-threatening	0	0
Subjects with AEs leading to treatment discontinuation	1 (7.1)	1 (2.2)
Subjects with AEs leading to drug interruption	0	2 (4.3)
Subjects with SAEs	0	5 (10.9)
Subjects with Grade 3/4 AEs	0	2 (4.3)
Subjects with AE leading to death	0	0

Source: Table 2.5.5 p80 of the submission, Table 12.4 p79 of Attachment 8 CSR

AE = adverse event; n = size of subsample; N = total sample size; SAE = serious adverse event

When summarising number of events, a subject with multiple events within a category was counted multiple times in that category. When summarising number and percentage of subjects, a subject with multiple events within a category was counted only once in that category. When summarising number of subjects with related (serious) AEs, AEs with relationship of related, possibly related, and missing were counted. Subjects with Grade 3/4 TEAEs included the 'Severe' and 'Life-Threatening' categories. If subjects only had one event with missing severity, then the subject was summarised in the "Missing" category. "Missing" was not displayed in the table if no subjects fall into this category. Safety set includes participants who received at least one dose in Part A or Part B.

## **Benefits/harms**

6.19 Study 122 was a non-comparative study. As such, it was not possible for a quantitative comparison of the benefits and harms of lumacaftor/ivacaftor and BSC. Accordingly, a benefits/harms table has not been presented.

## **Clinical claim**

6.20 The submission described lumacaftor/ivacaftor plus BSC as superior in terms of efficacy and comparable in terms of safety compared to BSC alone.

6.21 The submission claimed that it was both plausible and reasonable to anticipate that lumacaftor/ivacaftor would have a positive impact on lung function in younger patients given the reduction in SwCl seen in Study 122, which was considered to be an indicator of treatment effect for patients 1 to less than 2 years of age. Study 122 was a single arm study and therefore it does not provide direct evidence to inform a comparison with BSC. Further, the longer-term magnitude of benefit of treatment in

the 1 to less than 2 years age group was unknown as the evidence presented was limited by the short duration (24 weeks) of Study 122.

- 6.22 The PBAC has previously considered submissions that requested the extension of the PBS listing for a CFTR modulator for CF patients (i) from those aged 6 and older to include those aged from 2 to 5 (ivacaftor PSD, November 2016 PBAC meeting, lumacaftor/ivacaftor PSD, July 2019 PBAC meeting); and (ii) from those aged 2 to 5 years to include the 1 to less than 2 years age group (ivacaftor PSD, March 2019 PBAC meeting). Given the aetiology of CF, difficulties in obtaining comparative data in infants with CF and the results presented for intermediate outcomes (including reduction in SwCl), the PBAC has previously concluded that it was plausible that the claim of superior efficacy and non-inferior safety of a CFTR modulator over BSC in patients aged 6 and older could be reasonably extrapolated to the 2 to 5 age group (paragraph 6.23, ivacaftor PSD, November 2016 PBAC meeting; paragraph 6.19, lumacaftor/ivacaftor PSD, July 2019 PBAC meeting;) and to the 1 to 2 year age group (paragraph 6.18, ivacaftor PSD, March 2019 PBAC meeting). The ESC considered that it was reasonable to assume there were benefits to starting treatment with lumacaftor/ivacaftor at a younger age (1-2 years), and that it was reasonable to extrapolate the clinical claims from older age cohorts.
- 6.23 The PBAC considered that the claim of superior comparative effectiveness was reasonable.
- 6.24 The PBAC considered that the claim of comparable comparative safety was reasonable.

### ***Economic analysis***

- 6.25 The submission presented a modelled cost-utility analysis (CUA) comparing lumacaftor/ivacaftor plus BSC with BSC for the F/F population aged 1 to less than 2 years.
- 6.26 The model was based on the Cox-proportional hazard survival model described in Liou et al (2001). This approach has been reviewed by the PBAC in other CFTR modulator submissions (Table 8, lumacaftor/ivacaftor PSD, July 2019; paragraph 6.27 ELX/TEZ/IVA PSD, November 2022).
- 6.27 The only two model inputs that were informed by Study 122 (patients aged 1 to less than 2) were mean weight-for-age z-score change from baseline and rate of discontinuation (8.5% over first 24 weeks). All other model inputs informing efficacy and safety for patients aged 1 to less than 2 years old were extrapolated from those based on older patient cohorts from Study 109 (aged 6 to 11 years), and TRAFFIC/TRANSPORT (aged  $\geq 12$  years).
- 6.28 A summary of the key components of the economic evaluation is presented in Table 6.

**Table 6: Summary of model structure, key inputs and rationale**

Component	Summary
Treatments	Cost-utility analysis
Time horizon	Lifetime, mean age at commencement of 1.5 years
Outcomes	Quality-adjusted life-years
Methods used to generate results	Individual patient microsimulation. Liou et al., 2001: CPH model used to apply the effect of nine risk factors (age, gender, ppFEV <sub>1</sub> , annual number of PExs, infections (Staphylococcus aureus [Sa] or Burkholderia cepacia [Bc]), diabetes mellitus, weight-for-age z-score, and pancreatic sufficiency status in patients with cystic fibrosis) 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 <sub>1</sub> status of normal (>90%), mild (70-90%), moderate (40-70%) and severe (<40%).
Cycle length	First two years of analysis: 4-week cycle length From two years onward: 52-week cycle length
Transition probabilities	Treatment effects based on RCT evidence: - improved ppFEV <sub>1</sub> (Study 109); - improved weight and weight-for-age z-scores (Study 122).  Baseline ppFEV <sub>1</sub> decline based on large longitudinal registry analyses (Konstan et al., 2007, de Boer et al., 2011).  Long-term reduction in the rROD in ppFEV <sub>1</sub> associated with LUM/IVA treatment was determined through the Managed Access Program (MAP) review of the long-term rROD of ppFEV <sub>1</sub> for LUM/IVA in Australia.  Baseline hazard function for survival derived from parametric survival function that fit the survival data from Irish CF data registry.  Individual patient characteristics (baseline values from the two RCTs Study 109 and TRAFFIC/TRANSPORT) were related to survival through a CPH model (Liou et al., 2001) which identified nine key characteristics of patients with CF that were found to predict survival, listed above.
Health related quality of life	ppFEV <sub>1</sub> level-based utility derived from a clinician survey: Normal=0.98, Mild=0.88, Moderate=0.67, Severe=0.37. Patients with lung transplant=0.81 (Anyanwu et al., 2002).
Software	Microsoft Excel making use of Visual Basic.

Source: Table 3.2.1, p96; Table3.5.12, p122 and Section 3.3.2 p100 of the submission.

CF=cystic fibrosis; CPH = Cox-proportional hazard; ICER = Incremental Cost-Effectiveness Ratio; LUM/IVA = lumacaftor/ivacaftor; MAP = managed access program; N/A= not applicable; PEx= pulmonary exacerbation; ppFEV<sub>1</sub> = predicted percent forced expiratory volume in 1 second; RCT=randomised controlled trial; rROD = relative rate of decline.

- 6.29 The economic model predicted that treatment with lumacaftor/ivacaftor from an age of 1.5 years would increase survival by 14.07 years (undiscounted) compared with BSC. The submission did not consider that at the age of 2 patients are currently eligible for lumacaftor/ivacaftor, which the evaluation considered would also be a more appropriate comparator. Additionally, the submission did not present a cost-effectiveness analysis of lumacaftor/ivacaftor followed by elexacaftor/tezacaftor/ivacaftor treatment once a patient reaches the age of 6 years old. The impact of sequential therapy on survival was not estimated in the economic model. The ESC acknowledged the challenges regarding data availability but considered modelling the benefit and cost of starting lumacaftor/ivacaftor between 1 and 2 years of age compared to starting > 2 years would have been appropriate for decision-making.
- 6.30 Consistent with other economic models for CFTR modulators, the submission assumed a 90% decrease in the price of lumacaftor/ivacaftor due to loss of exclusivity (LoE) and

generic medicines entering the market. The ESC has previously noted that price reductions due to LoE have not been realised as new treatments have become available before the price reduction occurs (paragraph 6.54, ELX/TEZ/IVA PSD, November 2022 PBAC meeting). The ESC noted the sensitivity of the model to this assumption, with a significant increase in the incremental cost effectiveness ratio (ICER) if LoE was set to zero.

6.31 The ESC noted that, consistent with other CFTR submissions, utilities were derived from a survey of seven Australian CF Centre directors using the EQ-5D-5L. The ESC recalled its previous consideration that the use of proxy completion in this way was likely to exaggerate differences between health states due to focusing effects and hence, reduce the ICER (paragraph 6.47, ELX/TEZ/IVA PSD, March 2021 PBAC meeting). The ESC again noted the utility value for normal ppFEV<sub>1</sub> was higher than the general Australian population utility value (paragraph 6.47, ELX/TEZ/IVA PSD, March 2021 PBAC meeting). Additionally, the ESC considered the EQ-5D-5L becomes less appropriate as the age of the population reduces and that overall, the approach taken to determine utilities remained inappropriate.

6.32 The model assumed a treatment compliance of 90% for all patients. The treatment compliance in Study 122 was 99.94% based on 46 patients.

6.33 The key drivers of the model are described in Table 7.

**Table 7: Key drivers of the model**

Description	Method/Value	Impact Base case: \$ [redacted] <sup>1</sup> per QALY gained
Time horizon	Lifetime time horizon. Treatment effect continued beyond 24-week study period.	High, favours LUM/IVA. Use of 20-year time horizon increased the ICER to \$ [redacted] <sup>2</sup> per QALY gained
Price reduction: LoE	LoE at 3.1 years, at which point the drug prices drop by 90%.	High, favours LUM/IVA. Use of 0% cost reduction increased the ICER to \$ [redacted] <sup>3</sup> per QALY gained
Treatment compliance	90% compliance rate applied in the model.	Moderate, favours LUM/IVA. Use of 99.94% treatment compliance increased the ICER to \$ [redacted] <sup>4</sup> per QALY gained.

Source: Table 3.5.23, pp132-133 of the submission and developed during evaluation.

ICER = incremental cost-effectiveness ratio; LoE = loss of exclusivity; LUM/IVA = lumacaftor/lvacaftor; QALY = quality-adjusted life-year.

The redacted values correspond to the following ranges:

<sup>1</sup> \$95,000 to < \$115,000

<sup>2</sup> \$155,000 to < \$255,000

<sup>3</sup> \$455,000 to < \$555,000

<sup>4</sup> \$115,000 to < \$135,000

6.34 The results of the CUA are presented in Table 8. The economic evaluation resulted in an incremental cost-effectiveness ratio (ICER) of \$95,000 to < \$115,00 per quality-adjusted life-year (QALY) gained for patients aged 1 to less than 2 years.

**Table 8: Results of the economic evaluation for patients initiating therapy aged 1 to less than 2**

	Lumacaftor/ivacaftor + BSC	BSC	Increment
Costs (\$)		\$685,577	
QALYs	13.64	11.38	2.26
<b>Incremental cost per QALY gained</b>			<sup>1</sup>

Source: Source: Table 3.5.22, p130 of the submission.  
 BSC = best supportive care; QALYs = quality-adjusted life-years.

The redacted values correspond to the following ranges:

<sup>1</sup> \$95,000 to < \$115,000

6.35 The results of key sensitivity analyses are summarised in Table 9. The results of the model were most sensitive to the assumptions of a shorter time horizon and removal of LoE.

**Table 9: Sensitivity analyses**

Analysis description	Incremental cost	Incremental effect (QALYs)	ICER	Change from base line, %
<b>Base case</b>		<b>2.26</b>	<sup>1</sup>	-
Discount rates (base case 5%)				
- Costs and benefits 0%		9.94	<sup>2</sup>	-35%
- Costs and benefits 3.5%		3.35	<sup>3</sup>	-22%
Effects				
- FEV <sub>1</sub> improvement due to LUM/IVA treatment increased to upper 95% CI value of 5.5% (base case = 3%)		2.65	<sup>3</sup>	-20%
- FEV <sub>1</sub> improvement due to LUM/IVA treatment decreased to lower 95% CI value of 0.5% (base case = 3%)		1.94	<sup>4</sup>	20%
Time horizon reduced from lifetime to 20 years		0.79	<sup>5</sup>	137%
Assumed 0% price reduction due to LoE (base case 90%)		2.26	<sup>6</sup>	428%
Treatment compliance rate of 99.94% in ages 1 to less than 2 (base case 90% to all ages).		2.26	<sup>4</sup>	14%

Source: Table 3.5.23, pp132-133 of the submission and developed during evaluation.

BSC = best supportive care; CI= confidence interval; FEV<sub>1</sub> = forced expiratory volume in 1 second; ICER= incremental cost-effectiveness ratio; LoE= loss of exclusivity; LUM/IVA= lumacaftor/ivacaftor; QALYs= quality-adjusted life-years

Rounding applies.

The redacted values correspond to the following ranges:

<sup>1</sup> \$95,000 to < \$115,000

<sup>2</sup> \$55,000 to < \$75,000

<sup>3</sup> \$75,000 to < \$95,000

<sup>4</sup> \$115,000 to < \$135,000

<sup>5</sup> \$155,000 to < \$255,000

<sup>6</sup> \$455,000 to < \$555,000

6.36 Overall, the ESC considered that the economic model presented was not informative for decision making as it did not compare the benefit and cost of starting lumacaftor/ivacaftor between 1 and 2 years of age to starting at 2 years of age and transitioning to ELX/TEZ/IVA at 6 years of age. However, the ESC acknowledged the challenges in providing a robust economic model for this comparison.

**Drug cost/patient/year**

6.37 A summary of the drug cost per patient is provided in Table 10. Based on the effective ex-manufacturer approved price (AEMP) of \$█ per pack the total cost per patient per year (AEMP) is estimated at \$█ assuming 99.94% compliance.

**Table 10: Drug cost per patient for lumacaftor/ivacaftor (based on effective price of \$█ per pack)<sup>a</sup>**

	Study based	Economic model	Financial estimates
Compliance	99.94%	90%	99.94%
Cost/patient/year	\$█	\$█	\$█

Source: Constructed using information in Table 3.5.19, Table 4.1.1 of submission

<sup>a</sup> The submission assumed 100% of scripts are dispensed via public hospital, therefore the effective price = dispensed price for maximum quantity

**Estimated PBS usage & financial implications**

6.38 This submission was not considered by DUSC. An epidemiological approach was used, similar to that presented in previous submissions (e.g., July 2019 for the F/F population aged 2 to 5 years old) for lumacaftor/ivacaftor. A summary of the estimated use and financial implications is provided in

6.39 Table 11.

6.40 The submission's estimates were based on an initial cohort of patients aged 1 to less than 2 years treated in Year 1 to Year 6, assuming 6.8% discontinuation in Year 1 and 14.9% in Year 2 and an estimated additional 0.5 incident patients in each year. This does not account for patients being eligible for lumacaftor/ ivacaftor once they turn 2 years of age. The evaluation considered it may have been more appropriate to account for a prevalent population of patients aged 1 to less than 2 years initiating treatment in each year (with the assumption that the financial cost of treatment from 2 years of age has already been accounted for). This approach is tested in a sensitivity analysis below.

6.41 The submission assumed that initiating patients would receive a full year of treatment in Year 1. The PBAC has previously noted that a more reasonable assumption was that initiating patients would commence treatment throughout the year, so that on average each patient received the equivalent of half a year's supply in the year in which they commence treatment (paragraph 6.42, lumacaftor/ivacaftor PSD, July 2019 PBAC meeting).

**Table 11: Key inputs for financial estimates**

Parameter	Value applied and source	Comment
Prevalent population	Prevalence of 33 patients in Year 1, based on the number of reported CF patients <2 years old with F508del mutation and assuming that 50% of those are between 1-2 years old (ACFDR annual reports 2013-2020 and bespoke report 2021)	Data provided by the DUSC Secretariat indicated that there were 49 patients in 2020, 24 patients in 2021 and 33 patients in 2022 with the F/F mutation receiving lumacaftor/ivacaftor scripts at 2 years of age (age at first script).
Incident patients	0.5 patients per year, based on estimated CF patient growth rate and the prevalent population.	The submission used the annual growth rate of the CF population (1.6% per annum) and applied it to the F/F population, which produced an estimated growth of 0.5 patients per annum
Uptake rate	90% based on local clinical opinion.	No source for this assumption was presented.
Discontinuation rate	6.8% in Year 1 and 14.9% in Year 2. Based on the PBAC previously accepting these discontinuation rates for LUM/IVA in F508del patients aged 2 and older (July 2018 PBAC meeting)	-
Compliance rate	99.94% (based on Study 122, Part B) and estimated 13.04 scripts per patient per year	The submission applied a 90% compliance rate in the economic evaluation. The PSCR stated that in the paediatric population compliance was high as it relied on parental supervision of the treatment. The PSCR stated that the difference between the compliance rate applied in the financial estimates and the economic evaluation was due to the economic evaluation including patients aged above 12 years.
MBS item	MBS item number 66512 - 4 services in Year 1, followed by 1 service per year thereafter for mandatory liver function test. MBS item number 104 - 2 services per year for ophthalmological visits.	-

Source: Compiled during evaluation using data from Table 4.1.1, p135, Table 4.2.4, 139, Table 4.2.5, p139, Table 4.3.3, p141, Table 4.8.1, p148 of the submission.

ACFDR = Australian Cystic Fibrosis Disease Registry; CF = cystic fibrosis; DUSC = Drug Utilisation Sub-Committee; F/F = F508del homozygous; LUM/IVA = lumacaftor/ivacaftor; MBS = Medicare Benefits Schedule; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PSCR = pre-sub-committee response

6.42 A summary of the estimated use and financial implications is provided in Table 12.

**Table 12: Estimated use and financial implications (effective price) – aged 1 to less than 2 years old**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients treated <sup>a</sup>	1	1	1	1	1	1
Number of scripts dispensed <sup>b</sup>	1	1	1	1	1	1
<b>Estimated financial implications of lumacaftor/ivacaftor</b>						
Cost to PBS/RPBS less copayments	2	2	2	2	2	2
<b>Net financial implications</b>						
Net cost to MBS	2	2	2	2	2	2
<b>Net cost to Government</b>	<b>2</b>	<b>2</b>	<b>2</b>	<b>2</b>	<b>2</b>	<b>2</b>

Source: Table 4.3.3, and Table 4.3.4, p141, Table 4.6.1 and Table 4.6.2, p146, Table 4.8.1, p148 of the submission.

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

<sup>a</sup> Estimated patient numbers as fulltime equivalent, including discontinuation rate in Year 1 6.8% and Year 2 14.7%.

<sup>b</sup> Assuming 13.04 per year as estimated by the submission.

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> \$0 to < \$10 million

- 6.43 The total cost to the PBS/RPBS of listing lumacaftor/ivacaftor was estimated to be \$0 to < \$10 million in Year 1 decreasing to \$0 to < \$10 million in Year 6 and totaling \$10 million to < \$20 million over the first 6 years of listing.
- 6.44 The submission presented sensitivity analyses testing a higher and lower number of prevalent patients (n=38 and n=28) as well as a 95% treatment compliance rate (Table 12).
- 6.45 Additional sensitivity analyses were conducted during the evaluation (Table 13) that:
- applied a 90% compliance rate, consistent with the economic evaluation. As noted in Table 12, the PSCR stated that the 90% compliance rate included patients who were aged older than 12 years for the majority of modelled time horizon; and
  - assumed 30 patients<sup>3</sup> aged 1 to less than 2 years initiated treatment each year with initiating patients receiving 6 months of treatment in Year 1 (to account for commencing treatment partway through the year as discussed in paragraph 6.41). The PSCR stated that this approach did not assume growth in the CF population.

Table 13: Sensitivity analysis, impact on net PBS/RPBS costs

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	% change over 6 years
<b>Base case</b>							
PBS/RPBS costs	1	1	1	1	1	1	-
<b>Sensitivity analyses provided in submission</b>							
<b>Prevalent F/F population aged 1 to less than 2 years, base case 33 → 38</b>							
PBS/RPBS costs	1	1	1	1	1	1	+13%
<b>Prevalent F/F population aged 1 to less than 2 years, base case 33 → 28</b>							
PBS/RPBS costs	1	1	1	1	1	1	-16%
<b>Compliance, base case 99.94% → 95%</b>							
PBS/RPBS costs	1	1	1	1	1	1	-5%
<b>Compliance, base case 99.94% → 90% (#1)</b>							
PBS/RPBS costs	1	1	1	1	1	1	-10%
<b>An additional 30 patients aged 1 to less than 2 years initiating treatment each year with patients in Year 1 receiving 6 months of treatment (#2)</b>							
PBS/RPBS costs	1	1	1	1	1	1	+5%
<b>#1 and #2</b>							
PBS/RPBS costs	1	1	1	1	1	1	-6%

Source: Table 4.9.1, p148 of the submission; estimated during evaluation using the Excel workbook provided with the submission for Section 4: OKB1-2\_UCM-Release-3-Workbook-v108.xlsx.

F/F = F508del homozygous; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

The redacted values correspond to the following ranges:

<sup>1</sup> \$0 to < \$10 million

- 6.46 The ESC noted the sensitivity analyses presented above but considered that, overall, the approach taken in the submission to estimate the financial implications was reasonable.

<sup>3</sup> 33 prevalent patients x 90% uptake = 29.7 patients, rounded to 30 patients

### **Quality Use of Medicines**

- 6.47 The submission did not present a discussion of quality use of medicine issues. However, the administration of lumacaftor/ivacaftor granules mixed with food presents a wastage risk in very young children (potentially through regurgitation of the lumacaftor/ivacaftor mixed with food, or refusal to eat, and drug stability of only one hour when mixed) (paragraph 2.3, lumacaftor/Ivacaftor PSD, July 2019 PBAC meeting).

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

- 6.48 The submission proposed including the cost of lumacaftor/ivacaftor granules for the F/F population aged 1 to less than 2 years old under the same Risk Sharing Arrangement as applied to lumacaftor/ivacaftor for the older population. This would add the estimates for PBS use (at the effective price) to the existing caps for the CFTR modulators. The PSCR stated that the approach would be aligned with previous submissions where the forward estimates add the additional period of treatment to the existing financial cap, considering year on/off adjustments and first and second year discontinuations.

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended that the restriction for lumacaftor with ivacaftor granules be extended to include patients with cystic fibrosis (CF), homozygous for the F580del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, to include patients aged 1 to less than 2 years. The PBAC also recommended that an additional strength of granules (lumacaftor 75 mg/ivacaftor 94 mg) should be available under Section 100 (Highly Specialised Drugs Program) for use in this population. The PBAC considered that the supporting evidence was limited but acknowledged the difficulties in obtaining efficacy data from paediatric patients. Overall, the PBAC considered that the claim of superior efficacy over best supportive care (BSC) in patients aged from 1 to less than 2 years was biologically plausible and likely to be beneficial. The PBAC considered lumacaftor with ivacaftor was likely to be cost-effective at a unit price no higher than that of the current PBS listing (for patients  $\geq 2$  years of age). The PBAC advised that the current risk sharing arrangement (RSA) financial caps for lumacaftor/ivacaftor should be increased to accommodate patients commencing treatment earlier.
- 7.2 The PBAC acknowledged the consumer comments that strongly supported the expansion of the restriction to allow children aged 1 year and older to access lumacaftor/ivacaftor and described the potential benefits of treatment in terms of lung function and nutritional status.
- 7.3 The PBAC considered that the nomination of BSC as the comparator was reasonable for patients aged from 1 to less than 2 years.

- 7.4 The PBAC noted that the submission was based on one 24 week, single arm, open-label study (Study 122) that evaluated the safety and efficacy of lumacaftor/ivacaftor granules in patients aged 1 to less than 2 years. The PBAC noted that data comparing lumacaftor/ivacaftor to BSC was not available. The PBAC noted that, due to the difficulty in conducting spirometry in the population, Study 122 did not collect predicted forced expiratory volume in one second (ppFEV<sub>1</sub>), instead collecting data on the surrogate outcome of reduction in sweat chloride (SwCl). Study 122 demonstrated an overall reduction in SwCl from baseline at Week 24 which was comparable with results from similar studies in older patients. Overall, the PBAC considered that the reduction in SwCl was an indicator of treatment effect and it was biologically plausible that lumacaftor/ivacaftor would have a positive effect on lung function in children aged 1 to less than 2 years of age. However, the PBAC noted that the magnitude of benefit in terms of reducing the rate of lung function deterioration over both the short- and long-term as a result of commencing treatment from 1 year of age, compared with receiving BSC from 1 year of age and followed by lumacaftor/ivacaftor treatment starting at 2 years of age and the possibility of elexacaftor/tezacaftor/ivacaftor from 6 years of age, was unknown.
- 7.5 The PBAC considered that the claim that lumacaftor/ivacaftor had comparable safety to BSC was reasonable, noting that the incidence and type of adverse events were similar in older patients.
- 7.6 The PBAC noted the submission presented an estimate of the cost effectiveness of lumacaftor/ivacaftor in eligible patients who initiate treatment between the ages of 1 to 2 years, compared with BSC over a lifetime. While the PBAC considered this was not the comparison of interest for decision making for the current submission, it noted that the model was similar in structure to previous PBAC submissions for lumacaftor/ivacaftor and that the evidence required to inform the preferred comparison was not available. The PBAC noted that the majority of the efficacy and safety parameters used to inform the model were not based on the clinical evidence presented in the submission (Study 122), with data from older age cohorts instead used to populate the model and infer the comparative clinical benefit for lumacaftor/ivacaftor in the proposed age group (children aged 1 to less than 2 years). As a result, the PBAC considered that the base case incremental cost effectiveness ratio (ICER) was uncertain. However, based on the available evidence, the PBAC considered that it was plausible that lumacaftor/ivacaftor would be cost effective in this population at a unit price no higher than that for the  $\geq 2$  year old population.
- 7.7 The PBAC considered that the methodology for estimating the number of patients aged from 1 to less than 2 years treated with lumacaftor/ivacaftor and the estimated financial impact was reasonable.
- 7.8 The PBAC advised that the extended population should be included in the existing RSA for lumacaftor/ivacaftor with the financial caps increased to account for patients commencing treatment earlier.

7.9 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for lumacaftor/ivacaftor:

- a) Based on the available evidence the magnitude of benefit of initiating treatment with lumacaftor/ivacaftor at a younger age was not able to be quantified, and therefore the criteria of having a substantial and clinically relevant improvement in efficacy compared to initiating at an older age was not met;
- b) The treatment is expected to address a high and urgent unmet clinical need as the population currently has no alternative treatment option until they are at least 2 years of age;
- c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

7.10 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

8.1 Add new item, lumacaftor 75 mg/ivacaftor 94 mg sachets, and amend the existing listing for lumacaftor 100 mg/ivacaftor 125 mg and lumacaftor 150 mg/ivacaftor 188 mg sachets as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
<b>Lumacaftor + ivacaftor</b>					
lumacaftor 75 mg/ivacaftor 94 mg [28], 56	NEW (Public) NEW (Private)	1	56	5	Orkambi
lumacaftor 100 mg/ivacaftor 125 mg [28], 56	11866M (public) 11841F (private)				
lumacaftor 150 mg/ivacaftor 188 mg [28], 56	11851R (public) 11848N (private)				
<b>Restriction Summary variation / ToC variation</b>					
<b>Category / Program:</b> Section 100 – Highly Specialised Drugs Program [Public and Private Hospitals]					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – written non-immediate/delayed assessment by Services Australia					
<b>Indication:</b> cystic fibrosis					
<b>Treatment Phase:</b> Initial treatment					
<b>Treatment criteria:</b>					

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Must be treated by a specialist respiratory physician with expertise in cystic fibrosis or in consultation with a specialist respiratory physician with expertise in cystic fibrosis if attendance is not possible due to geographic isolation
AND
<b>Treatment criteria:</b>
Must be treated in a centre with expertise in cystic fibrosis or in consultation with a centre with expertise in cystic fibrosis if attendance is not possible due to geographic isolation
AND
<b>Clinical criteria:</b>
Patient must be homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene
AND
<b>Clinical criteria:</b>
The treatment must be given concomitantly with standard therapy for this condition.
AND
<b>Clinical criteria:</b>
The treatment must be the sole PBS-subsidised cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy for this condition.
AND
<b>Population criteria:</b>
Patient must be 1 year of age or older
<b>Prescribing Instruction:</b> This pharmaceutical benefit is not PBS-subsidised for this condition in a patient who is currently receiving one of the strong CYP3A4 inducers outlined in the Product Information.
<b>Prescribing Instruction:</b> The authority application must be in writing and must include: (1) a completed authority prescription; and (2) a completed Cystic Fibrosis Authority Application Supporting Information Form; (3) details of the pathology report substantiating the patient being homozygous for the F508del mutation on the CFTR gene - quote each of the: (i) name of the pathology report provider, (ii) date of pathology report, (iii) unique identifying number/code that links the pathology result to the individual patient; and (4) current CYP3A4 inhibitors, CYP3A4 inducers and IV antibiotics.
<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
<b>Administrative Advice:</b> Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a> Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at <a href="http://www.servicesaustralia.gov.au/hpos">www.servicesaustralia.gov.au/hpos</a> Or mailed to: Services Australia Complex Drugs Reply Paid 9826 Hobart TAS 7001
<b>Administrative Advice:</b> For the purposes of this restriction, CFTR modulators, regardless if they are available as a single drug or in combination, are currently: elexacaftor, ivacaftor, lumacaftor, tezacaftor.
<b>Administrative Advice:</b> Special Pricing Arrangements apply

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
<b>Lumacaftor + ivacaftor</b>					
lumacaftor 75 mg/ivacaftor 94 mg [28], 56	NEW (Public) NEW (Private)				
lumacaftor 100 mg/ivacaftor 125 mg [28], 56	11866M (public) 11841F (private)	1	56	5	Orkambi
lumacaftor 150 mg/ivacaftor 188 mg [28], 56	11851R (public) 11848N (private)				
<b>Restriction Summary variation/ ToC variation</b>					
<b>Category / Program:</b> Section 100 – Highly Specialised Drugs Program [Public and Private Hospitals]					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – written non-immediate/delayed assessment by Services Australia					
<b>Indication:</b> cystic fibrosis					
<b>Treatment Phase:</b> Continuing treatment					
<b>Treatment criteria:</b>					
Must be treated by a specialist respiratory physician with expertise in cystic fibrosis or in consultation with a specialist respiratory physician with expertise in cystic fibrosis if attendance is not possible due to geographic isolation					
<b>AND</b>					
<b>Treatment criteria:</b>					
Must be treated in a centre with expertise in cystic fibrosis or in consultation with a centre with expertise in cystic fibrosis if attendance is not possible due to geographic isolation					
<b>AND</b>					
<b>Clinical criteria:</b>					
Patient must have previously received PBS-subsidised treatment with this drug for this condition					
<b>AND</b>					
<b>Clinical criteria:</b>					
The treatment must be the sole PBS-subsidised cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy condition					
<b>AND</b>					
<b>Clinical criteria:</b>					
The treatment must be given concomitantly with standard therapy for this condition.					
<b>AND</b>					
<b>Population criteria:</b>					
Patient must be 1 year of age or older					
<b>Prescribing Instructions:</b> This pharmaceutical benefit is not PBS-subsidised for this condition in a patient who is currently receiving one of the strong CYP3A4 inducers outlined in the Product Information.					
<b>Prescribing Instructions:</b> The authority application must be in writing and must include: (1) a completed authority prescription; and (2) a completed Cystic Fibrosis Authority Application Supporting Information Form; (3) current CYP3A4 inhibitors, CYP3A4 inducers and IV antibiotics.					
<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised					
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.					

	<p><b>Administrative Advice:</b> Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a> Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at <a href="http://www.servicesaustralia.gov.au/hpos">www.servicesaustralia.gov.au/hpos</a> Or mailed to: Services Australia Complex Drugs Reply Paid 9826 Hobart TAS 7001</p>
	<p><b>Administrative Advice:</b> For the purposes of this restriction, CFTR modulators, regardless if they are available as a single drug or in combination, are currently: elexacaftor, ivacaftor, lumacaftor, tezacaftor.</p>
	<p><b>Administrative Advice:</b> Special Pricing Arrangements apply</p>

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

## 9 Context for Decision

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

## 10 Sponsor's Comment

Vertex welcomes the positive recommendation by the Pharmaceutical Benefits Advisory Committee (PBAC), to extend the listing of Orkambi® (lumacaftor/ivacaftor) to include children with cystic fibrosis ages 1 - < 2 years who have two F508del mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

With this recommendation, approximately 35 children in Australia with two copies of the F508del mutation will have access to a medicine to treat the underlying cause of their disease.