

## 5.08 LUMACAFTOR WITH IVACAFTOR, Sachet containing granules, lumacaftor 100 mg with ivacaftor 125 mg, lumacaftor 150 mg with ivacaftor 188 mg, Orkambi<sup>®</sup>, Vertex Pharmaceuticals (Australia) Pty Ltd.

### 1 Purpose of Application

- 1.1 The submission requested a Section 100, Authority Required listing for lumacaftor/ivacaftor granules for treatment of cystic fibrosis (CF) patients aged 2 years and older who are homozygous for the F508del mutation in the CF transmembrane conductance regulator (CFTR) gene. The key components of the submission are presented in Table 1.

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

Component	Description
Population	CF patients aged 2–5 years who are homozygous for the F508del mutation in the CFTR gene.
Intervention	Lumacaftor/ivacaftor, weight-based dosing: <ul style="list-style-type: none"> <li>Weight &lt;14 kg: One sachet of granules (containing lumacaftor 100 mg/ivacaftor 125 mg) PO q12h (lumacaftor 200 mg/ivacaftor 250 mg total daily dose).</li> <li>Weight ≥14 kg: One sachet of granules (containing lumacaftor 150 mg/ivacaftor 188 mg) PO q12h (lumacaftor 300 mg/ivacaftor 376 mg total daily dose).</li> </ul>
Comparator	BSC plus placebo.
Outcomes	Absolute change from baseline in: LCI <sub>2.5</sub> & LCI <sub>5.0</sub> ; sweat chloride; ppFEV <sub>1</sub> ; nutritional status (BMI, BMI-for-age z-score, weight, weight-for-age z-score, stature, stature-for-height). Pulmonary exacerbation measures. Absolute change in FE-1; IRT.
Clinical Claim	Lumacaftor/ivacaftor plus BSC is superior in terms of effectiveness compared with BSC alone. Lumacaftor/ivacaftor plus BSC is non-inferior in terms of safety compared to BSC alone.

Source: Table 1.1.1 of the submission pp26-27.

Abbreviations: BMI = body mass index; BSC=best supportive care; CF=cystic fibrosis; CFTR=cystic fibrosis transmembrane conductance regulator; FE-1=faecal elastase 1; FEV=forced expiratory volume; IRT=immunoreactive trypsinogen; LCI<sub>2.5</sub>=lung clearance index at 2.5% of starting concentration; LCI<sub>5.0</sub>=lung clearance index at 5.0% of starting concentration; PO = oral administration; ppFEV<sub>1</sub>= percent predicted forced expiratory volume in one second; q12h = every 12 hours.

- 1.2 This is the first submission for lumacaftor/ivacaftor granules. Lumacaftor/ivacaftor tablets are currently subsidised on the PBS for the treatment of CF patients aged 6 years and older who are homozygous for the F508del mutation in the CFTR gene.
- 1.3 The submission presented one pivotal trial (Study 115) to support the clinical claim compared with best supportive care (BSC). However, Study 115 was an open-label, non-comparative study, and the submission did not present evidence of the comparative efficacy or safety versus BSC.

## 2 Requested listing

2.1 The proposed listing is summarised in Table 2.

**Table 2: Proposed PBS listing**

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
LUMACAFTOR/IVACAFTOR Lumacaftor 100 mg/ivacaftor 125 mg granules, 56 sachets Lumacaftor 150 mg/ivacaftor 188 mg granules, 56 sachets	1	5	\$ [REDACTED]	Orkambi®	Vertex Pharmaceuticals
<b>Section 100 (Highly Specialised Drugs Program) Authority required</b>					
Treatment of cystic fibrosis in patients aged ≥2 years who are homozygous for the F508del mutation in the CFTR gene					

- 2.2 The submission requested listing for patients aged 2 years and over. This would potentially allow use of the granules in children aged 6 years and over who might otherwise qualify for access to lumacaftor/ivacaftor tablets. However, the cost per mg associated with the granules is higher than that associated with the tablets such that use of granules in a child over five years of age who could otherwise access lumacaftor/ivacaftor tablets would be less cost-effective. The evaluation considered that it may be appropriate to restrict use of the granules to children between the ages of 2 and 5 years. The PSCR stated the sponsor would be open to discussing an arrangement similar to ivacaftor granules, where the additional cost is rebated for paediatric patients aged more than 5 years old.
- 2.3 Administration of lumacaftor/ivacaftor granules mixed with food presents a wastage risk in very young children (potentially through regurgitation of/refusal to eat lumacaftor/ivacaftor mixed with food, and drug stability of only one hour when mixed). This would be anticipated to affect the cost-effectiveness of lumacaftor/ivacaftor in clinical practice in this setting insofar as more drug would be required to achieve the claimed effect. The PSCR stated that “based on experience with the Australian clinical trial patients in this age group (2–5 years), Vertex are not aware of an issue regarding inability to swallow the treatment. Furthermore, the sweat chloride results...clearly indicate that the treatment is being swallowed and absorbed effectively.”
- 2.4 No special pricing arrangements were proposed in the submission; however, consistent with the Risk Sharing Arrangement (RSA) under the current Deed of Agreement for lumacaftor/ivacaftor, the submission proposed a reduction in the gross cost of lumacaftor/ivacaftor granules via a subsidisation cap. While the submission stated that the intent of the proposed RSA was to achieve a price of \$ [REDACTED] per patient per year, the ESC noted there was a significant risk that the Government would pay a higher amount per full-time equivalent (FTE) patient (see *Financial Management – Risk Sharing Arrangements* in section 6 for further details).

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

### 3 Background

#### Registration status

3.1 **TGA status at time of PBAC advice:** Lumacaftor/ivacaftor granules were TGA registered on 21 June 2019 for the treatment of cystic fibrosis in patients aged 2 to 5 years who are homozygous for the F508del mutation in the CFTR gene.

#### Previous PBAC considerations

3.2 The PBAC has considered submissions for lumacaftor/ivacaftor for use in patients aged 12 years and older on four separate occasions, and for use in patients 6 years and older on one occasion. The submission for lumacaftor/ivacaftor for patients aged 6 to 11 years and the fourth submission for patients aged 12 years and over were considered concurrently and recommended by the PBAC in July 2018.

3.3 A frame of reference was prepared for the current submission (2 to 5 year olds) with the evidence previously considered by the PBAC for those aged 6 years and older; see Table 3.

**Table 3: Comparison of key clinical and safety data across lumacaftor/ivacaftor (re)submissions**

Component	(Re)submissions March 2016, November 2016, July 2017 and July 2018: aged ≥ 6 years	Current submission: July 2019: 2 to 5 years
Indication	CF patients homozygous for the F508del mutation in the CFTR gene aged: <ul style="list-style-type: none"> <li>6 to 11 years; and</li> <li>12 and older.</li> </ul>	CF patients homozygous for the F508del mutation in the CFTR gene aged: <ul style="list-style-type: none"> <li>2 to 5 years.</li> </ul>
Dose and recommended course of treatment	<ul style="list-style-type: none"> <li>6 to 11 years: 2 tablets q12h (luma 200 mg/iva 125 mg)</li> <li>12 and older: 2 tablets q12h (luma 100 mg/iva 125 mg)</li> </ul>	Weight based dosing, 2 to 5 years: <ul style="list-style-type: none"> <li>&lt;14 kg: 1 sachet q12h (luma 100 mg/iva 125 mg)</li> <li>≥14 kg: 1 sachet q12h (luma 150 mg/iva 188 mg)</li> </ul>
Comparator	Best supportive care. The PBAC accepted that BSC is the appropriate comparator for the 12+ population (lumacaftor/ivacaftor (12+), PSD July 2018, paragraph 5.1.	Best supportive care.
Clinical Evidence	<ul style="list-style-type: none"> <li>6 to 11 years: Study 109 RCT: luma/iva vs. placebo, 24 wks; Study 011: Phase II open-label study.</li> <li>12 and older: TRAFFIC &amp; TRANSPORT pooled RCT: luma/iva vs. placebo, 24 wks; PROGRESS: extension study, 96 wks.</li> </ul>	<ul style="list-style-type: none"> <li>2 to 5 years: Study 115: non-comparative, open-label study, 24 wks.</li> </ul>
Key effectiveness data	Absolute change (relative to placebo) from baseline in ppFEV <sub>1</sub> for lumacaftor/ivacaftor treated patients: <p>At week 24:</p> <ul style="list-style-type: none"> <li>6 to 11 years: 3% pts</li> <li>12 and older: 2.8% pts</li> </ul> <p>At extension Week 96 (up to 120 weeks of continuous treatment):</p> <ul style="list-style-type: none"> <li>12 and older: 0.5% pts</li> </ul>	Primary outcomes for Study 115 was safety and PK. Efficacy outcomes were secondary outcomes. <p>Absolute change from baseline in ppFEV<sub>1</sub> for lumacaftor/ivacaftor treated patients (n=17), at week 24: 0.5%.</p>
Key safety data	Pooled TRAFFIC/TRANSPORT, Study 109	Study 115

Component	(Re)submissions March 2016, November 2016, July 2017 and July 2018: aged ≥ 6 years	Current submission: July 2019: 2 to 5 years								
	Patients (%)	TRAFF/TRANS ≥ 12 (%)		Study 109 6 to 11 y		Patients (%)	L 100 / I 125 N=19	L 150 / I 188 N=41	Pooled	
		L/I N=369	PBO N=370	L/I N=103	PBO N=101					
		AEs	95.1	95.9	95.1	97.0	AEs	100	97.6	98.3
		SAEs	17.3	28.6	12.6	10.9	SAEs	10.5	4.9	6.7
		AEs → treat disc	4.6	1.6	2.9	2.0	AEs → treat disc.	0	7.3	5.0
Clinical claim	<p>Lumacaftor/ivacaftor plus BSC compared with BSC alone is:</p> <ul style="list-style-type: none"> <li>Superior in terms of effectiveness.</li> <li>Non-inferior in terms of safety.</li> </ul> <p>The PBAC considered the claim that lumacaftor/ivacaftor slows the rate of decline in ppFEV<sub>1</sub> beyond 24 weeks, compared with patients treated with BSC, was not adequately supported by the resubmission [para 6.39 of the July 2017 PSD].</p>	<p>Lumacaftor/ivacaftor plus BSC compared with BSC alone is:</p> <ul style="list-style-type: none"> <li>Superior in terms of effectiveness.</li> <li>Non-inferior in terms of safety.</li> </ul> <p>The submission did not provide evidence on the comparison of treatment with lumacaftor/ivacaftor + BSC compared with BSC.</p>								
Economic evaluation	<p>Cost-utility model (cost/QALY)</p> <ul style="list-style-type: none"> <li>6 to 11 years; [redacted] (restricted to 6 to 11 years) (≥ 6 years of age)</li> <li>12 and older: [redacted]</li> </ul>	<p>Cost-utility model (cost/QALY)</p> <ul style="list-style-type: none"> <li>2 to 5 years; [redacted] (restricted to 2 to 5 year olds) (≥ 2 years of age)</li> </ul>								
Financial implications	<p>Overall impact on government health budget: Age 6 years and older:</p> <ul style="list-style-type: none"> <li>With cap: \$ [redacted] in year 1 increasing to \$ [redacted] in year 5.</li> </ul>	<p>Overall impact on Government health budget:</p> <ul style="list-style-type: none"> <li>With cap: \$ [redacted] in year 1 increasing to \$ [redacted] in year 6.<sup>a</sup></li> <li>Without cap: \$ [redacted] in year 1 increasing to \$ [redacted] in year 6.</li> </ul>								
PBAC decision	<p>Recommended at July 2018 PBAC meeting (also considered at PBAC meetings: March 2016, November 2016, July 2017) with a managed access plan, a special pricing arrangement to give effect to a price of \$ [redacted] per patient per year and caps on total expenditure in line with estimated utilisation.</p>	<p>NA</p>								

Source: Lumacaftor/ivacaftor (12+), PBAC minutes July 2018; Lumacaftor/ivacaftor, PSD March 2016; Lumacaftor/ivacaftor, PSD November 2016; Lumacaftor/ivacaftor, PSD July 2017; Lumacaftor/ivacaftor (6-11y), PSD July 2018.

Abbreviations: AE = adverse event; BSC = best supportive care; CF=cystic fibrosis; CFTR=cystic fibrosis transmembrane conductance regulator; ICER = incremental cost-effectiveness ratio; L/I = lumacaftor ivacaftor tablets; L 100/I 125 = lumacaftor 100 mg/ivacaftor 125 mg; L 150/I 188 = lumacaftor 150 mg/ivacaftor 188 mg; luma = lumacaftor; lva = ivacaftor; mg=milligram  
 NA = not applicable; PBAC = Pharmaceutical Benefits Advisory Committee; PBO = placebo; PK = pharmacokinetics; ppFEV<sub>1</sub>= percent predicted forced expiratory volume in one second; QALYs = quality-adjusted life-years; q12h = every 12 hours; RCT = randomised controlled trial; SAE = serious adverse event.

<sup>a</sup> The proposed cap on Government expenditure applies to the first four years of listing only. Accordingly, the estimated impact on the Government health budget in the fifth and sixth years is the same with and without the cap.

3.4 The PBAC has previously considered submissions for ivacaftor granules as monotherapy for the treatment of CF patients that have a G551D mutation or other gating (class III) mutation in the CFTR gene for patients aged 2 to 5 years (November 2016 and January 2017) and 12 to <24 months (March 2019). While noting the ivacaftor submissions were for a different CF patient population, the evaluation

considered the basis of these recommendations may provide additional context for the current submission for lumacaftor/ivacaftor granules.

- In November 2016, the PBAC deferred the submission for ivacaftor granules for patients aged 2 to 5 years. [REDACTED], given the difficulty in demonstrating the incremental benefit and therefore cost-effectiveness of earlier treatment with ivacaftor. However, the PBAC did not agree with the submission's claim that [REDACTED]. The PBAC was of the view that it would be possible to negotiate an alternative arrangement whereby the intended outcome could be achieved, for example, by requiring a [REDACTED] % rebate for patients aged 2 to 5 years (ivacaftor minutes, November 2016, paragraph 7.7). In January 2017, the PBAC subsequently recommended listing ivacaftor granules and including patients aged 2-5 years in the ivacaftor RSA, and that [REDACTED] (ivacaftor minutes, November 2016, addendum).
- In March 2019, the PBAC recommended extending the listing of ivacaftor granules to include patients aged 12 to <24 months (ivacaftor minutes, March 2019, paragraph 7.1). The PBAC considered that the magnitude of the incremental benefit in commencing treatment with ivacaftor at a younger age was unknown and, therefore, the incremental cost-effectiveness of commencing treatment in this age group was uncertain. Noting the difficulty in demonstrating cost-effectiveness of earlier treatment with ivacaftor, the PBAC advised that the extension to the listing of ivacaftor should be implemented [REDACTED] (ivacaftor minutes, March 2019, paragraph 7.7).

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

## **4 Population and disease**

- 4.1 CF is an autosomal recessive disease caused by mutations in the CFTR gene that primarily affects the pulmonary and digestive systems.
- 4.2 Similar to submissions in patients with CF aged 6 years and older, this submission proposed that lumacaftor/ivacaftor be administered in addition to BSC in patients aged 2 years and older who are homozygous for the F508del mutation on the CFTR gene.
- 4.3 The proposed clinical place in therapy was in line with the full indication for lumacaftor/ivacaftor included in the TGA approved PI for children aged over 2 years.
- 4.4 The ESC noted that most patients with CF are diagnosed prior to 3 months of age; accordingly, extending the listing for lumacaftor/ivacaftor to patients aged 2 to 5 years would result in incident patients beginning treatment at 2 years of age (instead of 6 years of age, as per the current listing).

*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 choice of comparator was consistent with previous lumacaftor/ivacaftor submissions in older populations (lumacaftor/ivacaftor PSD, July 2018, paragraph 5.1). However, the submission did not consider that as the majority of CF patients will be diagnosed in their infancy, the requested PBS listing represents an earlier start to therapy (potentially from 2 years of age) as compared with the current PBS listing for lumacaftor/ivacaftor (potentially from 6 years of age). Therefore, the ESC considered that the appropriate comparator would have been BSC from 2-5 years of age, followed by lumacaftor/ivacaftor treatment starting at 6 years of age, as per the current listing for lumacaftor/ivacaftor tablets.

## 6 Consideration of the evidence

### *Sponsor hearing*

6.1 There was no hearing for this item.

### *Consumer comments*

6.2 The PBAC noted and welcomed the input from individuals (419) via the Consumer Comments facility on the PBS website. The comments described the potential for improved health outcomes associated with commencing treatment with lumacaftor/ivacaftor at a younger age.

### *Clinical trials*

6.3 The submission was based on one 24-week open label trial evaluating the safety and efficacy of lumacaftor/ivacaftor granules (L 100 mg/l 125 mg; L 150 mg/ l 188 mg); Study 115 (Part A (N=19); Part B (N=41)). There were no head-to-head randomised trials available comparing lumacaftor/ivacaftor plus BSC with BSC for the requested ages. The selection of the studies for inclusion in the submission was appropriate.

6.4 Details of the trial presented in the submission are provided in theTable 4 below.

**Table 4: Trials and associated reports presented in the submission**

<b>Trial ID</b>	<b>Protocol title/ Publication title</b>	<b>Publication citation</b>
Study 115	A Phase 3, two-part, open-label study to evaluate the safety and pharmacokinetics of lumacaftor/ivacaftor combination therapy in subjects aged 2 through 5 years with cystic fibrosis, homozygous for the F508del-CFTR mutation. McNamara J, McColley SA, Owen CA, et al. 2018. A two-part, Phase 3, single-arm study to evaluate the safety and pharmacokinetics (PK) of lumacaftor/ivacaftor (LUM/IVA) combination therapy in patients (pts) aged 2 to 5 years with cystic fibrosis (CF) homozygous for the F508del-CFTR mutation.	Internal study report., 5 January 2018  Journal of Cystic Fibrosis 2018;17(Supplement 3):S2-S3

Source: Table2.2.1 p57 of the submission.

6.5 The key features of Study 115 are summarised in Table 5.

Table 5: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
<b>Lumacaftor/ivacaftor + BSC</b>					
Study 115	Part A (N=12) Part B (N=60)	OL, MC, 2-part study Part A: 15 days; Part B: 24 weeks.  Weight based dose: <14 kg: L 100 mg/l 125 mg q12h; ≥14 kg: L 150 mg/l 188 mg q12h.	High	Aged 2 to 5 years with CF homozygous for the F508del mutation.	Absolute change from baseline in: LCI <sub>2.5</sub> & LCI <sub>5.0</sub> ; sweat chloride; ppFEV <sub>1</sub> ; nutritional status (BMI, BMI-for-age z-score, weight, weight-for-age z-score, stature, stature-for-height). Pulmonary exacerbation (PEX) measures; Absolute change in pancreatic function measures (FE-1; IRT).

Abbreviations: BMI = body mass index; BSC=best supportive care; CF=cystic fibrosis; CFTR=cystic fibrosis transmembrane conductance regulator; FE-1=faecal elastase 1; FEV=forced expiratory volume; IRT=immunoreactive trypsinogen; LCI<sub>2.5</sub>=lung clearance index at 2.5% of starting concentration; LCI<sub>5.0</sub>=lung clearance index at 5.0% of starting concentration; MC=multi-centre; OL=open label; PEX=pulmonary exacerbations; PO = oral administration; ppFEV<sub>1</sub>= percent predicted forced expiratory volume in one second; q12h = every 12 hours.

6.6 The following issues were identified with regards to the study design, analysis and its implications for the interpretation of the evidence:

- Study 115 was a non-randomised, non-comparative, open label trial. The study was designed to demonstrate the safety, pharmacokinetics and pharmacodynamics of lumacaftor/ivacaftor in children aged 2 to 5 years. The overall risk of bias was high due to its non-randomised and open-label nature.
- While the study included two parts (Part A and Part B), the number of patients in Part A that transitioned into Part B was unknown; the two parts should thus be considered as stand-alone.
- The sample size was small which influences the robustness of the effects measures and the results were only available for up to 24 weeks of treatment (whereas CF is a chronic condition).
- The absence of a comparator group means it was not possible to assess the comparative safety/efficacy outcomes for lumacaftor/ivacaftor in this patient group.

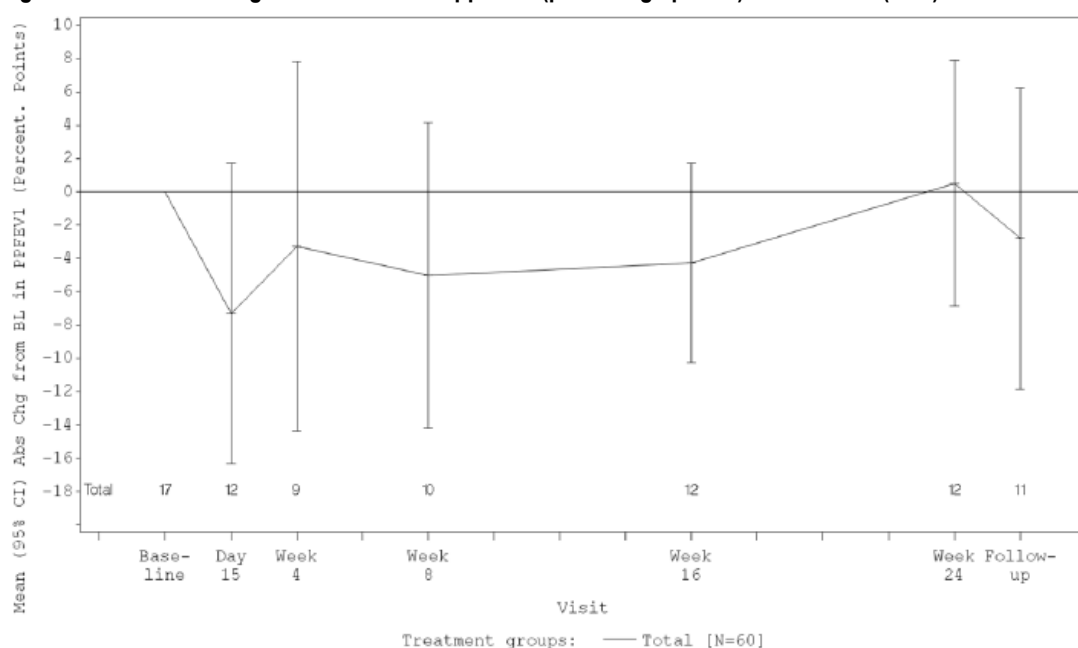
### **Comparative effectiveness**

6.7 Efficacy was reported as a secondary outcome from Part B in Study 115; the primary outcome was safety. The results from Study 115 showed that treatment with lumacaftor/ivacaftor resulted in an improvement in the:

- Absolute change in ppFEV<sub>1</sub> at week 24 compared with baseline (0.5%, 95% CI: -6.9, 7.9; p=0.8829, n=12) (Figure 1). The submission noted that this change was not significant, potentially due to the limited data available, arising from the difficulty of obtaining spirometry measurements in young children (N=12). This was reasonable.
- LCI<sub>2.5</sub> after 24 weeks compared with baseline (mean absolute change: -0.58 units; p=0.0559) (Figure 2). The result was not statistically significant, although the submission asserted this was due to the study not being powered for this outcome.

This was reasonable. The submission claimed that the change in LCI<sub>2.5</sub> exceeded the minimal clinically important difference (MCID; a change of between 0.5-1.0 units based on expert opinion; see p73 and 76 of the submission). While the change was numerically within the proposed MCID, it was not statistically significant and the corresponding confidence intervals spanned values outside of the MCID. At the follow-up visit (after the two-week washout period), LCI<sub>2.5</sub> returned to the approximate baseline level (Figure 2.5.1). The PBAC previously considered that there is no established minimum clinically important change in LCI and it is uncertain how improvements in LCI<sub>2.5</sub> may contribute to patient relevant outcomes that lead to improvements in survival or quality of life (Lumacaftor/ivacaftor (6-11y) PSD, July 2018, paragraph 6.36).

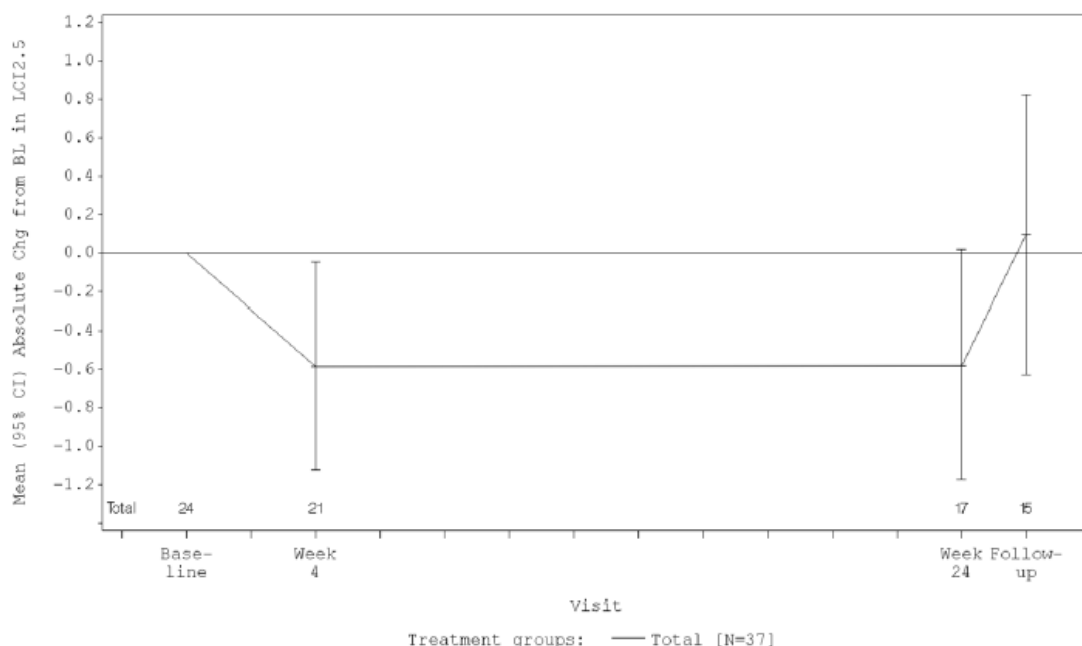
Figure 1: Absolute change from baseline in ppFEV1 (percentage points) at each visit (FAS)



Source: Figure 2.5.3 p78 of the submission; Study 115 CSR Figure 11-15 p100

Abbreviations: Abs = absolute; BL = baseline; Chg = change; CI = confidence interval; FAS = full analysis set; IVA = ivacaftor; LUM = lumacaftor; N = number; ppFEV1 = percent predicted forced expiratory volume in one second; q12h = every 12 hours

Figure 2: Absolute change from baseline in LCI2.5 at each visit (LCI substudy set)



Source: Figure 2.5.1 p77 of the submission; Study 115 CSR Figure 11-16 p102

Abbreviations: Abs = absolute; BL = baseline; Chg = change; CI = confidence interval; FAS = full analysis set; IVA = ivacaftor; LCI = lung clearance index; LCI2.5 = number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value; LUM = lumacaftor; N = number; q12h = every 12 hours.

6.8 Other results from the secondary outcomes from Part B in Study 115 showed 24 weeks of treatment with lumacaftor/ivacaftor resulted in a statistically significant improvement from baseline in the absolute change in:

- Sweat chloride (-31.7 mmol/L,  $p < 0.0001$ ).
- Nutritional status measures (BMI, weight and stature): BMI of 0.27 kg/m<sup>2</sup> ( $p = 0.0091$ ); BMI-for-age z-score of 0.29 ( $p = 0.0003$ ); Weight of 1.4 kg ( $p < 0.0001$ ); Weight-for-age z-score of 0.26 ( $p < 0.0001$ ); Stature of 3.6 cm ( $p < 0.0001$ ); Stature-for-age z-score of 0.09 ( $p = 0.0104$ ).
- Pancreatic function measures: FE-1 of 52.6 µg/g ( $p = 0.0012$ ); IRT of -129.9 ng/mL ( $p = 0.0009$ ).

6.9 The benefits of treatment with lumacaftor/ivacaftor as reported from Study 115 should be interpreted with caution due to the small sample size and the lack of a comparable placebo control group.

6.10 The PSCR claimed that the observed changes in sweat chloride would not occur as a result of standard treatment and indicate a consistent effect on CFTR function, as observed in other Phase 3 studies in older patients. The ESC considered that the observed change in sweat chloride indicated at best a moderate effect on the function of the CFTR when compared with the change observed in the clinical trials for ivacaftor granules in CF patients aged 2-5 years with a CFTR gating mutation (a different CF

patient population) at 24 weeks (-46.9 mmol/L, p<0.0001) and 108 weeks (-54.7 mmol/L, p<0.0001) (ivacaftor PSD, November 2016, paragraph 6.10).

- 6.11 A comparison of efficacy results for the use of lumacaftor/ivacaftor in older children with those for children aged 2 to 5 years was not presented in the submission. A summary of the efficacy outcomes from the pivotal studies for lumacaftor/ivacaftor was conducted during the evaluation and presented in Table 6. Younger patients have numerically higher results than older patients with respect to nutritional status outcomes (weight-for-age z-scores, stature-for-age z-scores and BMI-for-age z-scores). The number of PEx events per person is higher for patients aged 2 to 5 years compared with patients aged 6 to 11 years.

**Table 6: Comparison of efficacy outcomes across the lumacaftor/ivacaftor trials and age groups**

Age group Study ID	2 – 5 years			6 – 11 years	≥ 12 years
	Study 115 L 100 mg/ I 125mg	Study 115 L 150 mg/ I 188 mg	Study 115 Pooled	Study 109	TRAFFIC/ TRANSPORT
	24 wks	24 wks	24 wks	24 wks	24 wks
	N=19	N=41	N=60	N=204	N=369
ppFEV <sub>1</sub> LS Mean <sup>a</sup> (SE), % points	n=0 NA	n=12 0.5 (11.6)	n=12 0.5 (11.6)	n=103 2.5 (0.9)	n=369 2.49 (0.379)
LCI <sub>2.5</sub> LS Mean <sup>a</sup> (SE), units	n=3 0.27 (0.48)	n=14 -0.76 (1.19)	n=17 -0.58 (1.16)	N=103 -1.01 (0.13)	NR
Sweat chloride LS Mean <sup>a</sup> (SE), mmol/L	n=18 -33.5 (14.5)	n=31 -30.7 (14.0)	n=49 -31.7 (14.1)	n=103 -20.0 (1.0)	NR
BMI-for-age z-score LS Mean <sup>a</sup> (SE), units	n=19 0.36 (0.67)	n=38 0.26 (0.53)	n=57 0.29 (0.57)	n=103 0.08 (0.04)	NR
BMI LS Mean <sup>a</sup> (SE), kg/m <sup>2</sup>	n=19 0.22 (0.78)	n=38 0.29 (0.75)	n=57 0.27 (0.75)	n=103 0.38 (0.07)	n=369 0.37 (0.28, 0.47)
Weight-for-age z-score LS Mean <sup>a</sup> (SE), units	n=19 0.44 (0.52)	n=38 0.17 (0.36)	n=57 0.26 (0.44)	n=103 0.06 (0.02)	n=369 0.10 (0.02)
Weight LS Mean <sup>a</sup> (SE), kg	n=19 1.4 (0.7)	n=38 1.5 (1.0)	n=57 1.4 (0.9)	n=103 2.0 (0.1)	NR
Stature-for-age z-score LS Mean <sup>a</sup> (SE), units	n=19 0.19 (0.32)	n=38 0.04 (0.19)	n=57 0.09 (0.25)	N=103 0.03 (0.02)	NR
Stature LS Mean <sup>a</sup> (SE), cm	n=19 4.1 (1.4)	n=38 3.4 (1.0)	n=57 3.6 (1.2)	n=103 2.9 (0.1)	NR
<b>Pulmonary exacerbation</b>					
Event rate per pt year, Mean (SD)	0.54 (1.51)	1.07 (1.77)	0.90 (1.70)	NR	NR
Patients with events, n (%)	3 (16)	15 (37)	18 (30)	20 (19)	NR
Events, n	5	20	25	24	152
Events per person	1.67	1.33	1.39	1.20	NR

Source: Study 115: Table 2.5.2 p78, Table 2.5.1 p76, Table 2.5.3 p79, Table 2.5.4 p80-81, Table 2.5.5 p83, Table 2.5.6 p85 of the submission; Study 109: Lumacaftor/ivacaftor (6-11 y), PSD July 2018 Table 5, Table 6: Lumacaftor/ivacaftor (6-11 y) COM Table 2.5.3, Table 2.5.10, Table 2.5.11, Table 2.5.12; TRAFFIC/TRANSPORT and PROGRESS: Lumacaftor/ivacaftor, PSD March 2016 Table 4, Table 5; Lumacaftor/ivacaftor, PSD July 2017 Table 5, Table 7, Table 9; 5.04 lumacaftor/ivacaftor COM Table B.6.4, Table B.6.5; Lumacaftor/ivacaftor (6-11 y), July 2018 COM; Lumacaftor/ivacaftor March 2016 COM.

Abbreviations: BMI = body mass index; BSC=best supportive care; CF=cystic fibrosis; CFTR=cystic fibrosis transmembrane conductance regulator; CI = confidence interval; FEV=forced expiratory volume; LCI = lung clearance index; LCI<sub>2.5</sub>=lung clearance index at 2.5% of starting concentration; LCI<sub>5.0</sub>=lung clearance index at 5.0% of starting concentration; L/I = lumacaftor/ivacaftor; LS = least squares; NR = not reported; PBO = placebo; PEx = Pulmonary exacerbation; ppFEV<sub>1</sub>= percent predicted forced expiratory volume in one second; SD = standard deviation; SE = standard error.

<sup>a</sup> LS Mean values reported show the change from baseline to 24 weeks.

- 6.12 The PSCR stated that the main objective of treatment is to minimise the rate of lung function deterioration. In patients aged 12 years and older, treatment with lumacaftor/ivacaftor resulted in a 42% reduction in the rate of ppFEV<sub>1</sub> decline over 96 weeks, compared with a matched control group (Konstan et al 2017). The PSCR stated that, when stratified by age, there was a 45% reduction for 12 to 17-year old patients, and a 41% reduction for ≥18-year old patients. While the PSCR acknowledged that the decline in the older cohort is not directly applicable to the younger cohort, the PSCR suggested that this evidence suggests that the longer-term impact of slowing the decline in FEV<sub>1</sub> is consistent across age groups and that treating patients early before significant structural damage occurs may yield improved long-term benefits with lumacaftor/ivacaftor [compared with treatment onset from 6 years of age].

### **Comparative harms**

- 6.13 The submission did not present a comparison of safety outcomes for lumacaftor/ivacaftor + BSC versus BSC.
- 6.14 A summary of the AEs for lumacaftor/ivacaftor is presented in Table 7. In Part B of Study 115, the majority of patients had AEs that were considered mild (48.3%) or moderate (41.7%) in severity. Three (5.0%) patients had at least one AE that led to lumacaftor/ivacaftor discontinuation (elevated transaminases, n=3). Three (5.0%) patients had at least one AE that led to lumacaftor/ivacaftor interruption (elevated transaminases, n=2; constipation, n=1). Four (6.7%) patients had SAEs (infective PEx of CF, n=2; gastroenteritis viral, n=1; constipation, n=1). The most common AEs were cough (63.3%), vomiting and pyrexia (28.3% each), rhinorrhoea (25.0%), nasal congestion and upper respiratory tract infection (16.7% each), increased ALT (13.3%), ear infection and constipation (11.7% each), and diarrhoea and increased AST (10.0% each).

Table 7: Summary of key adverse events in Study 115

	Part A (15 days)			Part B (24 weeks)		
	L 100 mg/ I 125 mg (N=4)	L 150 mg/ I 188 mg (N=8)	Total (N=12)	L 100 mg/ I 125 mg (N=19)	L 150 mg/ I 188 mg (N=41)	Total (N=60)
Total number of AEs	11	9	20	131	236	367
Patients, n (%)						
Any AEs	4 (100.0)	6 (75.0)	10 (83.3)	19 (100.0)	40 (97.6)	59 (98.3)
AEs by maximum severity						
Mild	4 (100.0)	5 (62.5)	9 (75.0)	7 (36.8)	22 (53.7)	29 (48.3)
Moderate	0	1 (12.5)	1 (8.3)	10 (52.6)	15 (36.6)	25 (41.7)
Severe	0	0	0	2 (10.5)	3 (7.3)	5 (8.3)
Life-threatening	0	0	0	0	0	0
AEs leading to treat. discontinuation	0	1 (12.5)	1 (8.3)	0	3 (7.3)	3 (5.0)
AEs leading to treatment interruption	0	0	0	2 (10.5)	1 (2.4)	3 (5.0)
SAEs	0	0	0	2 (10.5)	2 (4.9)	4 (6.7)
Related SAEs	0	0	0	1 (5.3)	0	1 (1.7)
AEs leading to death	0	0	0	0	0	0

Source: Table 2.5.1 p76 and Table 2.5.9 p91 of the submission.

Abbreviations: AE = adverse event; L 100 mg/I 125 mg = lumacaftor 100 mg/ivacaftor 125 mg; L 150 mg/I 188 mg = lumacaftor 150 mg/ivacaftor 188 mg; N = number of patients; SAE = serious adverse event.

## Benefits/harms

6.15 Study 115 was a non-comparative study. As such, it is not possible to present a comparative benefits-to-harms summary.

## Clinical claim

6.16 The submission described lumacaftor/ivacaftor plus BSC as superior in terms of effectiveness compared with BSC alone and non-inferior in terms of safety compared with BSC alone. Previous submissions of lumacaftor/ivacaftor in patients aged 6 years and older with CF who are homozygous for the F508del mutation (March 2016; July 2017; July 2018) have also described lumacaftor/ivacaftor as superior in terms of comparative effectiveness and equivalent in terms of comparative safety over BSC.

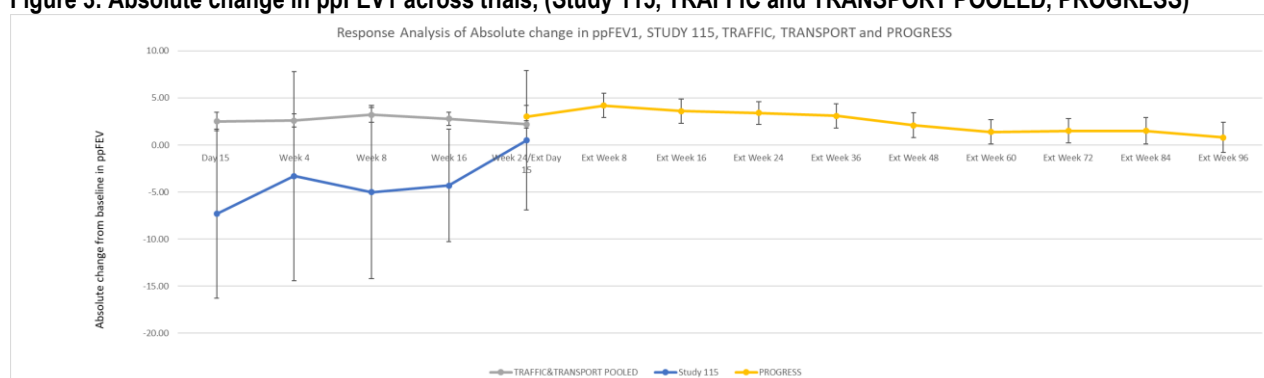
6.17 Given the absence of a comparator group and the small number of patients in Study 115, the therapeutic conclusion presented was not adequately supported by the evidence presented in Section 2 of the submission. The following should be noted with respect to interpreting the evidence presented:

- Study 115 was a non-randomised, non-comparative and open label study. As such, the study results were subject to considerable uncertainty.
- The absence of a comparator group in Study 115 means that positive results in terms of changes in ppFEV<sub>1</sub>, LCI<sub>2.5</sub>, weight gain and other outcomes should be interpreted with caution.
- Study 115 assessed the efficacy of lumacaftor/ivacaftor in terms of intermediate outcomes, collected over a short period of time (24 weeks). However, the

submission did not use these data to inform the comparison over the long-term, which is relevant as lumacaftor/ivacaftor may be used as a lifelong treatment.

- 6.18 The evaluation considered that the therapeutic conclusion with regard to clinical efficacy presented in the submission was not adequately supported by the evidence presented, particularly in the absence of long-term data. This is particularly relevant in light of the data from the PROGRESS study that demonstrated that the modest ppFEV<sub>1</sub> increase in lumacaftor/ivacaftor treated patients (12 years of age and older) was not maintained in the longer term, with the improvement from baseline not being statistically significant at extension week 96 (i.e. up to 120 weeks of treatment) (PROGRESS; see Figure 3) (lumacaftor/ivacaftor, PSD July 2017 paragraph 7.4).

**Figure 3: Absolute change in ppFEV1 across trials, (Study 115, TRAFFIC and TRANSPORT POOLED, PROGRESS)**



Abbreviations: Ext=extension, ppFEV<sub>1</sub>= percent predicted forced expiratory volume in one second

Source: Compiled by the evaluation based on Table 2.5.2 p78 of the submission; Table 11-4, p131 of CSR TRAFFIC; Table 11-5, p141 of CSR TRANSPORT; Table 11-2 p102 of CSR PROGRESS.

- 6.19 The ESC considered that given the aetiology of CF, difficulties in obtaining comparative data in this patient population, and the results of intermediate outcomes from Study 115 (including reduction in sweat chloride), the claim of superior efficacy compared with BSC alone was biologically plausible. However the ESC noted the magnitude of benefit over both the short-term and a lifetime was unknown as the supportive evidence was limited by the lack of a control, the short duration (24 weeks) of Study 115 and lack of ppFEV<sub>1</sub> outcomes (which were previously considered the primary endpoint upon which to assess the efficacy of ivacaftor).
- 6.20 The ESC considered the claim of non-inferior safety to BSC was reasonable noting there were no major safety signals with lumacaftor/ivacaftor in the study presented or in older patients.
- 6.21 The PBAC considered that the claim of superior effectiveness compared with BSC was biologically plausible. However, the PBAC noted that the magnitude of benefit of commencing treatment at a younger age, in terms of reducing the rate of lung function deterioration over both the short- and long-term, was unknown (see paragraph 6.19).
- 6.22 Based on data presented previously from older age groups, the PBAC considered that the claim of non-inferior safety compared with BSC was reasonable.

### **Economic analysis**

- 6.23 The economic evaluation presented was a cost-utility analysis (CUA). The structure of the model was the same as in the previous (re)submissions (March 2016, November 2016, July 2017, July 2018), which presented a CUA of lumacaftor/ivacaftor compared with BSC. The economic evaluation did not rely directly on the clinical data (efficacy and safety) presented in Section 2; data from older age cohorts were used to populate the model and infer the comparative clinical benefit for lumacaftor/ivacaftor in the proposed age group (children aged 2 to 5 years).
- 6.24 The ESC noted that the submission did not present an estimate of the incremental cost effectiveness of starting treatment with lumacaftor/ivacaftor from two years of age (early onset treatment) compared with BSC from 2-5 years, followed by lumacaftor/ivacaftor treatment starting at 6 years of age (as is currently funded via the PBS). The ESC considered that the magnitude of the incremental benefit in commencing treatment with lumacaftor/ivacaftor at a younger age was uncertain and, therefore, the incremental cost effectiveness of early onset treatment was uncertain.
- 6.25 The pre-PBAC response stated that an analysis of the incremental cost effectiveness of early onset treatment would require a higher evidentiary burden than that applied to other age-based sub-groups. The PBAC noted that while the submissions for ivacaftor granules for eligible CF patients aged 2 to 5 years and 12 to <24 months also did not present the incremental cost effectiveness of early onset, [REDACTED]  
[REDACTED] By comparison, the current submission requested an increase in the current lumacaftor/ivacaftor subsidisation caps through the current RSA by over [REDACTED] for each of the remaining years of the current Deed of Agreement.
- 6.26 The key components of the economic evaluation are provided in Table 8.

**Table 8: Summary of model structure and rationale**

Component	Summary
Types of analysis	Cost utility analysis
Outcomes	Quality-adjusted life years
Time horizon	Base case analysis: lifetime vs. the following durations in the pivotal evidence: Patients aged 12+: 24 weeks (randomised) with 96 weeks of extension data (up to 120 weeks of treatment); Patients aged 6–11: 24 weeks (randomised) Patients aged 2–5: 24 weeks (non-randomised)
Method used to generate results	Individual patient microsimulation
Health states	Changes are recorded based on individual patient underlying risk factors. Health states based on ppFEV <sub>1</sub> 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 <sub>1</sub> 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 <sub>1</sub> post 24 weeks) and change in weight-for-age z-score. Baseline hazard function from Cystic Fibrosis Registry of Ireland 2013.
Utilities	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 3.1.1 of the submission pp99-100.

Abbreviations: CF=cystic fibrosis; CPH = Cox Proportional Hazards; N/A= not applicable; PEx= pulmonary exacerbation; ppFEV<sub>1</sub> = predicted percent forced expiratory volume in 1 second; RCT=randomised controlled trial.

- 6.27 The ESC noted that the model was similar in structure to that presented in previous PBAC submissions for lumacaftor/ivacaftor and a number of concerns persist including assumptions around ongoing effect, the application of the Liou et al algorithm to link clinical outcomes with risk, the validity of the Irish CF Registry data to model baseline risk, and the derivation of utility weights.
- 6.28 The inputs that changed compared with the July 2018 model included specifying a starting age of 2 years for the model cohort, the application of an intended annual price of ██████ per patient and an assumed treatment compliance of 99.20% for patients aged 2 to 5 years. The assumed rate of treatment compliance was the only model input that was informed by Study 115; by comparison, the July 2018 model assumed 90% compliance for patients aged 6 years and older.
- 6.29 The key model inputs defined by the PBAC in an alternative scenario at the July 2017 PBAC meeting (lumacaftor/ivacaftor (12+) PSD, July 2018 paragraph 6.52), and how they have been incorporated into the current submission, are summarised in Table 9.

**Table 9: Summary of the alternative scenario defined by PBAC in July 2017 and how it was addressed in this submission**

Component	PBAC Alternative Scenario	Current Submission Approach
Lumacaftor/ivacaftor cap and price adjustments	Removal of the 5% statutory price reduction and 90% generic price reduction. Removal of the proposed cap.	Price reductions were reinstated and applied to the intended annual price of \$ [REDACTED] per patient. Removal of price reductions and the cap was tested in sensitivity analyses in the evaluation.
Sustained clinical effect in ppFEV <sub>1</sub>	Assumed that the annual rate of decline in ppFEV <sub>1</sub> for lumacaftor/ivacaftor post 24 weeks was the same as that seen in BSC (i.e. a 0% decrease in the annual rate of decline in ppFEV <sub>1</sub> , relative to BSC).	The post 24 week decrease in the annual rate of decline in ppFEV <sub>1</sub> for lumacaftor/ivacaftor was set at 42%, relative to BSC. Varied to 25% and 75% decrease in the decline, relative to BSC in the submission, and 0% in sensitivity analyses in the evaluation.
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% applied to lumacaftor/ivacaftor. Assuming 75% of hospitalisations are due to PEx was applied in sensitivity analyses in the evaluation. The submission also assumed no reduction in PEx among children aged 2-11 years.

Abbreviations: BSC=best supportive care; CF=cystic fibrosis; PEx=pulmonary exacerbations; ppFEV<sub>1</sub> =percent predicted forced expiratory volume in one second.

Source: Compiled during the evaluation from the Lumacaftor/Ivacaftor, PSD July 2017, paragraph 6.57; Lumacaftor/Ivacaftor (12+), PSD July 2018, paragraph 6.52.

6.30 The drivers of the model are reported in Table 10; these are largely unchanged from the July 2018 resubmission of lumacaftor/ivacaftor for patients aged 12 years and older and the July 2018 submission for patients aged 6-11 years.

**Table 10: Key drivers of the model**

Description	Method/Value	Impact	ICER (\$/QALY) Base case: \$ [REDACTED]
Intended annual price per patient	Intended annual price of \$ [REDACTED] per patient, implemented through subsidisation caps, applied for lumacaftor/ivacaftor drug cost. Sensitivity analysis performed in the evaluation using the requested published price.	High, favours lumacaftor/ivacaftor	[REDACTED]
Time horizon	Treatment effect continued beyond 24-week trial period for lifetime. Sensitivity analysis: reduce time horizon to 5 years (and to the trial-based period).	High, favours lumacaftor/ivacaftor	5 years: [REDACTED] (Trial based: [REDACTED])
Modelled change in ppFEV <sub>1</sub> in lumacaftor/ivacaftor patients.	Decrease in the annual decline in ppFEV <sub>1</sub> after the first 24 weeks set to 42%, relative to BSC. Sensitivity analysis to set decline equivalent to BSC.	High, favours lumacaftor/ivacaftor	[REDACTED]
Assumption of 90% price reduction at patent expiry and F1 statutory price reduction.	90% price reduction at end of patent life and 5% statutory price reduction. Sensitivity analysis: price reductions removed.	High, favours lumacaftor/ivacaftor	[REDACTED]
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. Sensitivity analysis assuming 75% of hospitalisations are due to PEx.	Moderate, favours lumacaftor/ivacaftor	[REDACTED]
Discontinuation beyond 24 weeks	Assumed no discontinuation beyond 24 weeks. Sensitivity analysis assuming the same discontinuation rate applied throughout (post 24 weeks), and no discontinuation until post 96 weeks.	High, favours lumacaftor/ivacaftor	24 wks: [REDACTED] (96 wks: [REDACTED])

Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; PE = pulmonary exacerbation; ppFEV<sub>1</sub> = per cent predicted forced expiratory volume in one second; QALY = quality adjusted life year.  
Source: compiled during the evaluation.

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

6.31 The submission did not present a stepped analysis for the economic evaluation. The results of the CUA are presented in Table 11.

**Table 11: Results of the economic evaluation, lumacaftor/ivacaftor vs BSC**

Population	Costs			QALYs			ICER \$/QALY
	lumacaftor/ ivacaftor	BSC	Incremental	lumacaftor/ ivacaftor	BSC	Incremental	
Submission base case: CF patients aged 2 to 5 years	[REDACTED]	[REDACTED]	[REDACTED]	13.53	11.10	2.42	[REDACTED]
Submission scenario analysis: CF patients aged 2 years and older	[REDACTED]	[REDACTED]	[REDACTED]	8.66	6.66	2.01	[REDACTED]
CF patients aged 6 years and older	[REDACTED]	[REDACTED]	[REDACTED]	7.97	6.14	1.83	[REDACTED]

Abbreviations: BSC= best supportive care; ICER= incremental cost-effectiveness ratio; QALYs= quality-adjusted life-years.  
Source: Table 3.6.5 p134, Table 3.6.6 p135 of the submission and calculated during the evaluation using the patient filter function in the economic model workbook

The redacted table shows ICERs in the range of \$105,000/QALY - \$200,000/QALY.

- 6.32 The cost per QALY gained for patients initiating treatment between the ages of 2 to 5 years, compared with BSC, was estimated in the submission to be from \$105,000/QALY - \$200,000/QALY gained. By comparison, the ICER for all patients initiating treatment from 2 years of age, compared with BSC, was estimated to be from \$105,000/QALY - \$200,000/QALY gained. This difference arose because the analysis for the 2 to 5 year cohort assumed that this age cohort forms 100% of the treated population over time, while in the over 2 years cohort all patients are included (of which the 2 to 5 year cohort represents only 12% of the treated cohort). This indicates that the model is implicitly factoring higher cost-effectiveness ratios for older cohorts; lumacaftor/ivacaftor is less cost-effective in older individuals because they have fewer years to benefit from treatment.
- 6.33 The model incorporated a decline in ppFEV<sub>1</sub> in lumacaftor/ivacaftor patients beyond the 24-week trial period to a lifetime. This decline was informed by the longer-term ppFEV<sub>1</sub> data from the extension trial PROGRESS. Beyond 24 weeks, the model included a 42% decrease in the annual decline in ppFEV<sub>1</sub> in lumacaftor/ivacaftor treated patients, relative to BSC. At the July 2017 meeting, the PBAC sought to be informed of the impact on the cost-effectiveness of assuming that the decline in ppFEV<sub>1</sub> for patients treated with lumacaftor/ivacaftor was the same as BSC after 24 weeks (lumacaftor/ivacaftor (12+), PSD July 2018, paragraph 6.52). A sensitivity analysis setting the decrease in the decline to 0% of BSC was conducted during the evaluation (see Table 12) which increased the ICER to more than \$200,000/QALY gained.
- 6.34 The submission's base case included application of a 5% F1 statutory price reduction and a 90% price reduction after patent expiry (loss of exclusivity) to the intended annual price of \$ [REDACTED] per patient. The PBAC previously noted that application of these price reductions was inappropriate and inconsistent with the PBAC Guidelines (lumacaftor/ivacaftor (aged 12+ years) PSD, July 2017 paragraph 6.42; lumacaftor/ivacaftor (aged 6-11 years) PSD, July 2018 paragraph 6.49). During the evaluation, these price reductions were removed in sensitivity analyses (see Table 12) which increased the ICER to more than \$200,000/QALY gained.
- 6.35 Furthermore, there is a significant risk that the Government would pay a higher amount than [REDACTED] per FTE patient per year, as realisation of this price through subsidisation caps is dependent on estimated utilisation being achieved (see *Financial Management – Risk Sharing Arrangements* in section 6 for further details).
- 6.36 The impact of key sensitivity analyses conducted in the submission and during the evaluation are presented in Table 12. These show that the largest single impact on the ICER was due to the application of the proposed financial cap and associated price reductions.

**Table 12: Results of sensitivity analyses for the submission base case: patients initiating treatment between the ages of 2 to 5 years, compared with BSC**

Analysis description	Incre. cost (\$)	Incre. effect (QALYs)	ICER (\$/QALY gained)	% Variation
Base case		2.42		NA
<b>Sensitivity analyses conducted by the submission</b>				
<b>Costs/prices</b>				
Cost of CF disease management including BSC doubled		2.42		-66%
Cost of CF disease management including BSC halved		2.42		33%
<b>Effects</b>				
FEV1 improvement due to lumacaftor /ivacaftor treatment increased to upper 95% CI (2-11 years FEV1 improvement = 5.5%; 12 years+ FEV1 improvement = 3.8%)		2.76		-14%
FEV1 improvement due to lumacaftor /ivacaftor treatment decreased to lower 95% CI (2-11 years FEV1 improvement = 0.5%; 12 years+FEV1 improvement = 1.8%)		2.05		23%
Set decrease in annual decline in FEV1 in lumacaftor/ivacaftor treated patients to 75%, relative to BSC		4.49		-54%
Set decrease in annual decline in FEV1 in lumacaftor/ivacaftor treated patients to 25%, relative to BSC		1.59		56%
<b>Sensitivity analyses conducted during evaluation</b>				
No financial cap, use published price		2.42		344%
No reduction in price due to LOE and no F1 statutory price reduction		2.42		240%
No financial cap or price reduction due to LOE or F1 statutory price reduction		2.42		1079%
Cost of cystic fibrosis disease management in lumacaftor/ivacaftor arm same as BSC (set 61.5% to 0% reduction)		2.42		72%
Cost of Cystic fibrosis disease management in lumacaftor/ivacaftor arm; assuming 75% of hospitalisations are due to PEx		2.42		18%
PBAC alternative scenario (see Table 9)		0.62		4179%
PBAC alternative scenario with \$ cap		0.62		1197%
Set annual decline in FEV <sub>1</sub> in lumacaftor/ivacaftor treated patients to be the same as BSC (i.e. 0% decrease in the decline in FEV <sub>1</sub> , relative to BSC)	\$311,372	0.62	\$500,689	309%
Discontinuation: beyond 96 weeks (same as <24 weeks)		0.91		147%
Discontinuation: beyond 24 weeks (same as <24 weeks)		0.77		157%
Time horizon: reduced from lifetime to trial based period		0.003		10249%
Time horizon: reduce from lifetime to 5 years		0.04		6564%

Source: Table 3.7.1 p135-137 of the submission and calculated during the evaluation using the Section 3 economic workbook.

Abbreviations: BSC = best supportive care; CF = cystic fibrosis; CI = confidence interval; FEV<sub>1</sub> = forced expiratory volume in one second; ICER = incremental cost-effectiveness ratio; LOE = loss of exclusivity; PEx = pulmonary exacerbation; QALY = quality-adjusted life-years

The redacted table shows ICERs in the range from \$15,000/QALY to more than \$200,000/QALY.

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

6.37 The proposed published price is \$18,750 per 28-day pack resulting in a cost per patient per year of \$244,587.05 (\$18,750/56 sachets per pack \* 2 sachets per day \* 365.25

days per year). The submission proposed an annual price of \$ [REDACTED] per patient, intended to be achieved via subsidisation caps. Treatment is ongoing for the lifetime of the patient. A summary of the drug cost per patient of lumacaftor/ivacaftor is provided in Table 13.

**Table 13: Drug cost per patient for lumacaftor/ivacaftor**

	Trial dose and duration	Model	Financial estimates
Mean dose			
L 100 mg/ I 125 mg	lumacaftor 100 mg /lvacaftor 125 mg granules, q12h	lumacaftor 100 mg /lvacaftor 125 mg granules, q12h	lumacaftor 100 mg /lvacaftor 125 mg granules, q12h
L 150 mg/ I 188 mg	lumacaftor 150 mg /lvacaftor 188 mg granules, q12h	lumacaftor 150 mg /lvacaftor 188 mg granules, q12h	lumacaftor 150 mg /lvacaftor 188 mg granules, q12h
Mean duration	168 days	Lifetime (predicted survival: 49.72 years)	6 years <sup>a</sup>
Total daily dose			
L 100 mg/ I 125 mg	L 200 mg/ I 250 mg	L 200 mg/ I 250 mg	L 200 mg/ I 250 mg
L 150 mg/ I 188 mg	L 300 mg/ I 376 mg	L 300 mg/ I 376 mg	L 300 mg/ I 376 mg
Cost/patient/year	\$244,587	\$ [REDACTED]	\$ [REDACTED] per year for the first 4 years of listing; \$ [REDACTED] after the first 4 years following the end of the current Deed of Agreement for lumacaftor/ivacaftor.

Source: Figure 2.3.1 and Figure 2.3.2 pp58-59, Table 2.4.6, Table 2.4.7, Table 2.4.8, Table 2.4.9 pp68-69 and Table 4.6.1, p154 of the submission; Orkambi 2to5 cost effectiveness model March 2019, spreadsheets "Costs" and "Aggregated Results".

<sup>a</sup> Assumed 6.7% discontinue treatment within the first year of treatment and no discontinuations beyond the first year. 12 patients were assumed to discontinue in the first year, and no more patients discontinued post-Year 1 of listing.

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

6.38 This submission was not considered by DUSC. An epidemiological approach was used, similar to previous (re)submissions (March 2016, November 2016, July 2017, July 2018) for lumacaftor/ivacaftor compared with BSC. A summary of the estimated use and financial implications is provided in Table 14. The proposed cap was estimated to be higher than \$ [REDACTED] per patient from Years 1 to 4 of listing; there was no cap applied in Years 5 and 6 of listing.

**Table 14: Estimated use and financial implications<sup>a</sup>**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients treated	████	████	████	████	████	████
Number of scripts dispensed	████	████	████	████	████	████
<b>Estimated financial implications of lumacaftor/ivacaftor</b>						
Gross cost to PBS/RPBS						
Without Cap	████████	████████	████████	████████	████████	████████
With Cap	██████	██████	██████	██████	██████	██████
Co-payment	████	████	████	████	████	████
Net cost PBS/RPBS						
Without Cap	████████	████████	████████	████████	████████	████████
With Cap	██████	██████	██████	██████	██████	██████
<b>Net financial implications</b>						
Net cost to MBS						
Without Cap	████████	████████	████████	████████	████████	████████
With Cap	██████	██████	██████	██████	██████	██████
Overall impact on government health budgets						
Without Cap	████████	████████	████████	████████	████████	████████
With Cap	██████	██████	██████	██████	██████	██████
Gross cost/total pts <sup>b</sup>						
Without Cap	████████	████████	████████	████████	████████	████████
With Cap	██████	██████	██████	██████	██████	██████

Abbreviations: PBS = Pharmaceutical Benefits Scheme; MBS = Medicare Benefits Schedule; RPBS = Repatriation Pharmaceutical Benefits Scheme

Source: Table 4.2.8 p145, Table 4.2.11 p147 and Table 4.5.1, p150 of the submission.

a The total number of scripts (assuming full packs dispensed) and patient co-payment (\$12.22) were updated during the evaluation.

b Calculation does not apply whole patient numbers.

The redacted table shows that the total estimated number of patients over 6 years was less than 10,000, and the net cost to the PBS without and with cap would be from \$10 - \$60 million.

- 6.39 Drug utilisation each year may have been overestimated by the submission due to the issues discussed in paragraphs 6.40-43. In this context, the ESC noted that achieving the intended annual price of \$████ per patient via subsidisation caps implemented through an RSA is dependent on estimated utilisation being met.
- 6.40 The submission estimated that 185 patients would initially be eligible for treatment, then subsequently an average of 3 patients aged from 2 to 5 years would be eligible per year. The submission’s estimate of eligible prevalence may be overestimated, however, incidence is underestimated. The submission assumed that half of the patients that do not have a genotype registered on the ACFDR are homozygous for F508del. However, the requested listing restricts access only to patients who are homozygous for the F508del mutation; the number of eligible patients is overestimated using this approach. In 2017, there were 72 new diagnoses of CF, where 55 of those people diagnosed were less than one year of age. Incidence is underestimated as the submission assumed that diagnosis occurs at any age, however, the majority of patients with CF are diagnosed as infants (ACFDR 2019 p9).
- 6.41 The submission assumed a 100% uptake rate; however, the ESC considered that this was unlikely to be realised in practice.

- During the evaluation, a study examining the uptake of lumacaftor/ivacaftor following approval in the USA was identified<sup>1</sup>. Prescriptions were given to 19% of eligible children aged 6 to 11 years, and 61% of patients aged 12 years and older.
  - The PSCR acknowledged that the uptake of lumacaftor/ivacaftor in patients aged 2 to 5 years is likely to be lower than 100%. However, the PSCR also contended that prescription rates of lumacaftor/ivacaftor in the USA published by Sawicki et al (2018) do not reflect internal sales data held by the sponsor. The PSCR stated that based on current sales data, uptake of lumacaftor/ivacaftor in patients aged 2 to 5 years old is 68% in the US and 96% (66/69 patients) in Ireland.
- 6.42 The submission assumed that all initiating patients will start treatment on day 1 of each year. It cannot be assumed that all new patients likely to receive lumacaftor/ivacaftor annually will receive a full year of treatment, as this will be dependent on birth date and date of diagnosis. The PBAC 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 (lumacaftor/ivacaftor (aged 12+) PSD, July 2018, paragraph 6.68).
- 6.43 The submission assumed that patients could only discontinue therapy in the first year of their treatment, which may have overestimated utilisation in subsequent years. The ESC noted that data from PROGRESS showed that this is not realistic and that there will be a proportion of patients discontinuing treatment beyond the first year (lumacaftor/ivacaftor, PSD July 2017, paragraph 6.65).

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

- 6.44 The submission proposed an annual price of \$ [REDACTED] per patient, intended to be achieved via subsidisation caps implemented through an RSA, consistent with the intended annual price per FTE patient for lumacaftor/ivacaftor (of \$ [REDACTED]) in patients aged 6 years and older.
- 6.45 The PBAC was of the view that the use of subsidisation caps through the current Deed of Agreement for lumacaftor/ivacaftor for patients aged 6 years and older is associated with a significant risk that the Government would pay a higher amount than \$ [REDACTED] per FTE patient per year. This is because realisation of this price is achieved via subsidisation caps and therefore dependent on the estimated utilisation being achieved.

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<sup>1</sup> Sawicki, G. S., A. K. Fink, M. S. Schechter, D. R. Loeffler and N. Mayer-Hamblett (2018). "Rate and predictors of prescription of lumacaftor - Ivacaftor in the 18 months following approval in the United States." *J Cyst Fibros* 17(6): 742-746.

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

- 6.46 In March 2019, the PBAC noted that the advice from the Department regarding current utilisation of lumacaftor/ivacaftor tablets (for patients aged 6 years and older) indicated that Government expenditure per patient in Year 1 of listing is likely to be significantly higher than what was considered acceptably cost-effective (i.e. \$ [REDACTED] per FTE patient per year) in its July 2018 recommendation (tezacaftor/ivacaftor (F508del), PBAC minutes March 2019, paragraph 7.10). The PBAC therefore advised that it would be appropriate for the Department to pursue alternative arrangements through which the price of \$ [REDACTED] per FTE patient for tezacaftor/ivacaftor and lumacaftor/ivacaftor could be achieved, for example, such as through reducing the subsidisation caps in the current Deed of Agreement, or by implementing a Special Pricing Arrangement, as previously suggested in the July 2018 lumacaftor/ivacaftor recommendation.
- 6.47 The ESC considered that increasing the annual subsidisation caps for lumacaftor/ivacaftor under the current Deed to include the estimated 2 to 5 years patient population at \$ [REDACTED] per FTE patient would further increase the risk that the Government would pay a higher amount than \$ [REDACTED] per FTE patient per year for each year of listing, and as an average over the first four years of listing. In this regard, the ESC requested that the Department provide the PBAC with an update on utilisation of lumacaftor/ivacaftor since listing on the PBS on 1 October 2018 and an assessment of the likelihood of achieving the price of \$ [REDACTED] per patient in Year 1 of listing.
- 6.48 The Department reminded the PBAC that the subsidisation cap for Year 1 of listing was set based on [REDACTED] prescriptions (or [REDACTED] FTE patients receiving 11 prescriptions per year) being dispensed in Year 1 (see Table 15). Table 16 presents the number of prescriptions and government expenditure for lumacaftor/ivacaftor for the first seven months of listing.

**Table 15: Subsidisation caps for lumacaftor/ivacaftor by year of listing**

Year of listing	FTE patients	Prescriptions*	Subsidisation cap (\$ [REDACTED]/patient)	Minimum subsidisation cap if MAP conditions not met**
Year 1	[REDACTED]	[REDACTED]	[REDACTED]	-
Year 2	[REDACTED]	[REDACTED]	[REDACTED]	-
Year 3	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Year 4	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Year 5	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Source: Deed of Agreement for lumacaftor with ivacaftor

FTE = full-time equivalent.

\*Assuming 11 prescriptions per FTE patient per year.

\*\* [REDACTED].

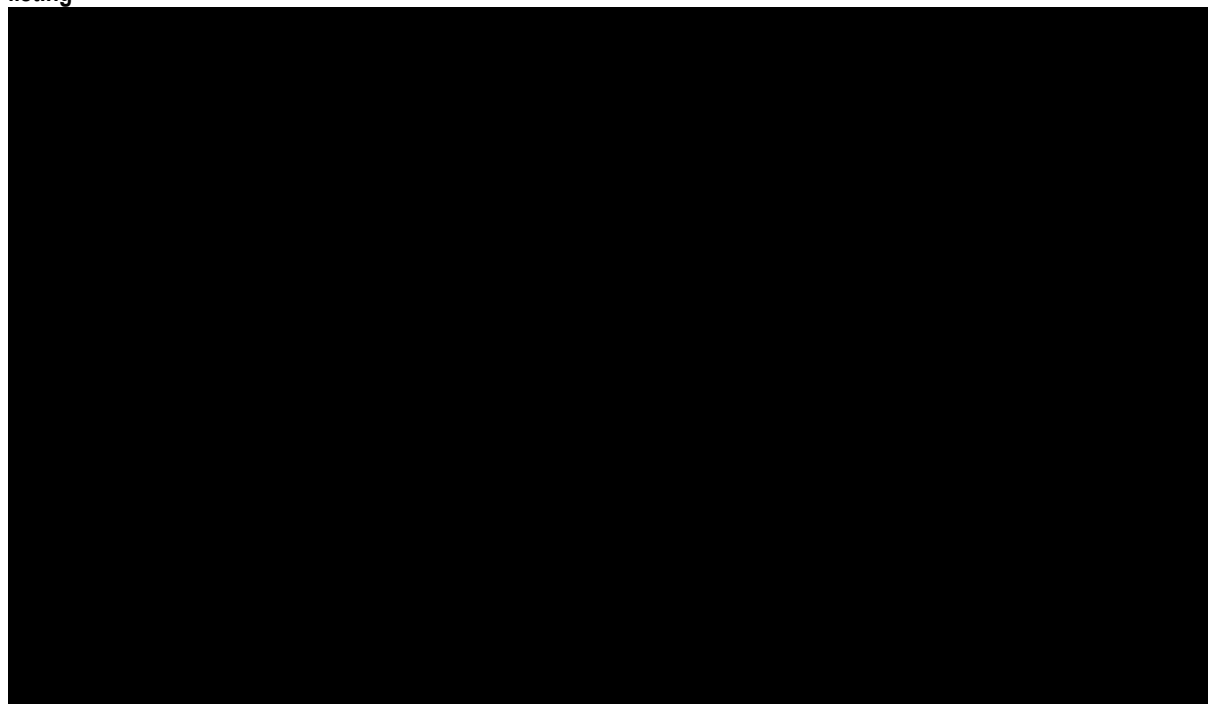
**Table 16: Utilisation of lumacaftor/ivacaftor (by month of processing), October 2018 to May 2019**

Month of processing	Prescriptions	Government Expenditure
Oct-18	3	\$56,237
Nov-18	214	\$4,009,838
Dec-18	347	\$6,502,590
Jan-19	419	\$7,841,791
Feb-19	636	\$11,906,888
Mar-19	639	\$11,971,828
Apr-19	932	\$17,455,396
<b>Total</b>	<b>3,190</b>	<b>\$59,744,569</b>

Data extracted on 11 June 2019.

6.49 Figure 4 illustrates four scenarios for utilisation for the remainder of Year 1 and the resulting government expenditure per FTE patient for Year 1 of listing (see legend). The most optimistic scenario (A), in which [REDACTED] patients (i.e. the entire estimated population of patients aged 6 years and older who are homozygous for F508del in the CFTR gene from the July 2018 PBAC submission) are treated in May 2019 and for the remainder of Year 1, Government expenditure per FTE patient would be around \$[REDACTED] – higher than the intended annual price of \$[REDACTED] per FTE patient.

**Figure 4: Lumacaftor/ivacaftor prescriptions based on month of processing (October 2018 to May 2019) with three scenarios for utilisation and the resulting government expenditure per FTE patient for the remainder of Year 1 of listing**



Data extracted on 11 June 2019.

6.50 The pre-PBAC response stated that the sponsor’s internal sales data align with the Department’s utilisation data. The sponsor claimed that the initiation of new patients on lumacaftor/ivacaftor has been lower than expected because four major CF centres have ceased initiating patients on lumacaftor/ivacaftor to wait for tezacaftor/ivacaftor

to become available. The pre-PBAC response estimated that the effective price per FTE patient would be around ██████ in Year 1 of listing and acknowledged this is greater than what was considered by the PBAC to be cost-effective in July 2018.

- 6.51 The PBAC noted the update on utilisation of lumacaftor/ivacaftor since its listing on 1 October 2018 provided by the Department and the pre-PBAC response. The PBAC considered that utilisation for Year 1 was likely to be similar to scenario C which would result in expenditure of around ██████ per patient for Year 1 (which was similar to the estimate in the pre-PBAC response). Accordingly, the PBAC considered that Government expenditure on lumacaftor/ivacaftor per patient in Year 1 is likely to be significantly higher than what was considered to be acceptably cost effective by the PBAC in July 2018 (paragraph 7.3, July 2018 minutes).
- 6.52 The pre-PBAC response claimed that the average annual price per FTE patient would be around \$█████ over the five years of the current Deed, but that this is dependent on the timing of listing tezacaftor/ivacaftor for the F508del homozygous CF patient population. The PBAC considered that an average annual price of \$█████ per patient was unlikely to be achieved, regardless of the timing of listing tezacaftor/ivacaftor. Nevertheless, the PBAC considered that if achieving the intended price of lumacaftor/ivacaftor was dependent on the timing of listing an alternative treatment for these patients, this further illustrated the risk of using subsidisation caps to achieve an intended price.

#### Managed Access Program (MAP)

- 6.53 The submission did not provide details about whether the sponsor intends that the requirements and implications of the current MAP for lumacaftor/ivacaftor for patients aged 6 years and older would also apply to the listing of lumacaftor/ivacaftor granules for 2 to 5 year olds.

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the Authority Required listing of a new presentation of lumacaftor with ivacaftor, in the form of granules, for the treatment of CF in patients aged 2 years or over who are homozygous for the F508del mutation in the CFTR gene. The PBAC recommendation was made on the basis that lumacaftor/ivacaftor granules should be available only under special arrangements under Section 100 (Highly Specialised Drugs Program). 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 BSC in patients aged 2 to 5 years was biologically plausible. However, the PBAC considered that as the incremental benefit of commencing treatment with lumacaftor/ivacaftor from an earlier age was unknown, the cost-effectiveness of commencing treatment earlier was also unknown. The PBAC advised that lumacaftor/ivacaftor granules should be listed for patients aged 2 years and older under the current RSA financial

caps for lumacaftor/ivacaftor without any increase to the subsidisation caps, such that the listing will not result in any additional cost to Government.

- 7.2 The PBAC acknowledged the consumer comments received, particularly from carers of patients with CF, that indicated strong support for access to treatment with lumacaftor/ivacaftor for eligible CF patients from a younger age.
- 7.3 The PBAC accepted the clinical place for lumacaftor/ivacaftor as an add-on to current BSC for patients aged 2 to 5 years, and considered that BSC (followed by treatment initiation from 6 years of age) was the appropriate comparator.
- 7.4 The submission was based on one 24 week non-randomised, non-comparative, open label study with a small sample size which evaluated the safety, pharmacokinetics and pharmacodynamics of lumacaftor/ivacaftor granules (Study 115). The PBAC noted that the submission did not present data comparing lumacaftor/ivacaftor to the nominated comparator. Instead the submission based its clinical claim largely on the basis of improvement from baseline to week 24 in secondary outcomes, including sweat chloride, nutritional status and pancreatic function measures. Overall, the PBAC considered that the claim of superior efficacy over BSC in patients aged 2 to 5 years was biologically plausible. 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 2 to 5 years of age (early onset treatment), compared with receiving BSC from 2 to 5 years of age followed by lumacaftor/ivacaftor treatment starting at 6 years of age (as is currently funded via the PBS), was unknown.
- 7.5 The PBAC noted that the tolerability of lumacaftor/ivacaftor in patients 2 to 5 years is similar to older patients.
- 7.6 The PBAC noted that the submission did not present an estimate of the incremental cost effectiveness of early onset treatment with lumacaftor/ivacaftor. The PBAC considered that as the magnitude of the incremental benefit in commencing treatment with lumacaftor/ivacaftor at a younger age was unknown, the incremental cost effectiveness of early onset treatment was unknown.
- 7.7 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 2 to 5 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 the argument in the pre-PBAC response that the evidence required to inform the preferred comparison was not available. The pre-PBAC response argued that the base case provided by the submission (patients initiating treatment between the ages of 2 to 5 years) and the scenario analysis (patients initiating from 2 years of age) should be sufficiently informative to the PBAC. The PBAC noted the model was similar in structure to previous PBAC submissions for lumacaftor/ivacaftor. The efficacy and safety parameters used to inform the model were not based on the clinical evidence presented in the submission (Study 115). Data from older age cohorts were instead

used to populate the model and infer the comparative clinical benefit for lumacaftor/ivacaftor in the proposed age group (children aged 2 to 5 years). The PBAC considered that the price applied in the model was the intended annual price of \$ [REDACTED] per patient which is unlikely to be achieved. In addition, the model inappropriately included a 5% statutory price reduction and 90% price reduction following loss of patent exclusivity. The PBAC noted the model results were highly sensitive to these assumptions. For example, if the 5% and 90% price reductions were removed the ICER increased to more than \$200,000/QALY gained. Accordingly, the PBAC considered that the ICER per QALY gained for the comparison presented by the submission was unacceptably high and uncertain at the intended annual price of \$ [REDACTED] per patient (which is unlikely to be achieved).

- 7.8 The PBAC considered that the submission's estimate of utilisation of lumacaftor/ivacaftor for this patient population was uncertain and likely overestimated, for the reasons outlined in paragraphs 6.40-43. In this context, the PBAC noted that achieving the intended annual price of \$ [REDACTED] per patient via subsidisation caps implemented through an RSA is dependent on estimated utilisation being met.
- 7.9 The PBAC advised that lumacaftor/ivacaftor granules should be listed for patients aged 2 years and older under the current RSA for lumacaftor/ivacaftor without any increase to the subsidisation caps, such that the listing will not result in any additional cost to Government.
- 7.10 The PBAC noted the advice from the Department regarding current utilisation of lumacaftor/ivacaftor and that the actual Government cost per patient in Year 1 of listing is likely to be significantly higher than what was considered acceptably cost-effective (i.e. \$ [REDACTED] per patient per year) in its July 2018 recommendation (see paragraph 6.52). The pre-PBAC response acknowledged that utilisation has been lower than originally forecast and claimed this was due to four major CF centres having ceased initiating patients on lumacaftor/ivacaftor to wait for tezacaftor/ivacaftor to become available. The PBAC considered the lower than expected uptake was surprising given the clinical need for an effective treatment for these eligible CF patients and the strong support from patients, clinicians and organisations for subsidised access to lumacaftor/ivacaftor. The PBAC also considered this illustrated the risk of using subsidisation caps to achieve an intended price. In this regard, the PBAC reiterated its advice from March 2019 (tezacaftor/ivacaftor (F508del), PBAC minutes March 2019, paragraph 7.10) that it would be appropriate for the Department to pursue alternative arrangements through which the annual price of \$ [REDACTED] per FTE patient (pending the outcome of the Managed Access Plan (MAP)) for both lumacaftor/ivacaftor and tezacaftor/ivacaftor could be achieved, for example, such as through reducing the subsidisation caps in the current Deed of Agreement, or by implementing a Special Pricing Arrangement (as previously suggested in the July 2018 lumacaftor/ivacaftor recommendation).

- 7.11 The PBAC considered that patients initiating on the granules aged 2 years and up to 6 years of age should not be included in the data collection and analysis to inform the MAP outcome, due to the difficulty in obtaining accurate ppFEV1 readings in this patient cohort.
- 7.12 The PBAC found that the three criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for lumacaftor/ivacaftor granules:
- a. Starting treatment with lumacaftor/ivacaftor at a younger age is not expected to provide a substantial and clinically relevant improvement in efficacy or reduction of toxicity over BSC (see paragraph 7.5).
  - b. Starting treatment with lumacaftor/ivacaftor at a younger age is not expected to address a high and urgent unmet clinical need.
  - 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.
- 7.13 The PBAC considered that lumacaftor/ivacaftor granules should not be treated as interchangeable with any other drugs.
- 7.14 The PBAC advised that lumacaftor/ivacaftor granules is not suitable for prescribing by nurse practitioners.
- 7.15 The PBAC recommended that the Early Supply Rule should apply.
- 7.16 The PBAC noted the submission is not eligible for an Independent Review, because the PBAC has made a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

### 8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
LUMACAFTOR WITH IVACAFTOR			Orkambi	Vertex Pharmaceuticals (Australia) Pty Ltd
lumacaftor 100 mg/ivacaftor 125 mg granule sachets, 56	1	5		
lumacaftor 150 mg/ivacaftor 188 mg granule sachets, 56	1	5		

<b>Category / Program:</b>	Section 100 – Highly Specialised Drugs Program
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	-
<b>Severity:</b>	-
<b>Condition:</b>	Cystic fibrosis
<b>PBS Indication:</b>	Cystic fibrosis
<b>Treatment phase:</b>	Initial treatment – new patients
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required – In Writing <input type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input type="checkbox"/> Streamlined
<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, AND 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>Clinical criteria:</b>	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.
<b>Population criteria:</b>	Patient must be aged 2 years or older.
<b>Prescriber Instructions:</b>	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 (3) a copy of the pathology report detailing the molecular testing for the patient being homozygous for the F508del mutation on the CFTR gene. The patient must be registered in the Australian Cystic Fibrosis Database Registry.
<b>Administrative Advice:</b>	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 <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a> Applications for authority to prescribe should be forwarded to: Department of Human Services

Public Summary Document – July 2019 PBAC Meeting

	<p>Complex Drugs Reply Paid 9826 HOBART TAS 7001</p> <p>No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.</p>
<b>Treatment phase:</b>	Continuing treatment
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required – In Writing <input type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	<p>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 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.</p>
<b>Clinical criteria:</b>	<p>Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND The treatment must be given concomitantly with standard therapy for this condition.</p>
<b>Population criteria:</b>	Patient must be aged 2 years or older.
<b>Prescriber Instructions:</b>	<p>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 Continuing Authority Application Supporting Information Form.</p>
<b>Administrative Advice:</b>	<p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a></p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p> <p>No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.</p>

## **9 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

## **10 Sponsor's Comment**

The sponsor had no comment.