7.16 LUMACAFTOR with IVACAFTOR
Tablet containing lumacaftor 200 mg with ivacaftor 125 mg
Orkambi®,
Vertex Pharmaceuticals (Australia) Pty Ltd.

1 Purpose of Application

1.1 The minor resubmission sought a Section 100 (Highly Specialised Drugs Program) Authority Required listing for lumacaftor with ivacaftor fixed dose combination (FDC) (referred to in this document as lumacaftor/ivacaftor) for the treatment of cystic fibrosis in patients aged 12 years and older who are homozygous for the F508 deletion mutation (F508del/F508del) in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

2 Requested listing

2.1 The minor resubmission requested the following listing. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

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

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
PBS Indication:	Cystic fibrosis
Restriction Level / Method:	☐ Restricted benefit ☒ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☐ Streamlined
Treatment criteria:	*Must be treated by a specialist respiratory physician with expertise in cystic fibrosis* *OR* *Must be treated in consultation with a specialist respiratory physician with expertise in cystic fibrosis if attendance is not possible due to geographic isolation* *AND* *Must be treated in a centre with expertise in cystic fibrosis* *OR* *Must be treated in consultation with a centre with expertise in cystic fibrosis if attendance is not possible due to geographic isolation*

Clinical criteria:	Patient must be homozygous for the F508del mutation in the *cystic fibrosis transmembrane conductance regulator* (CFTR) gene, AND *Patient must have a sweat chloride value of greater than or equal to 60 mmol/L;OR* *Patient must have at least 2 CF-causing mutations* *AND* *Patient must have a FEV1 of ≥40% and ≤90% of predicted normal for age, sex, and height* *AND* *Patient must have experienced chronic sinopulmonary disease; OR* *Patient must have experienced gastrointestinal abnormalities; OR* *Patient must have experienced nutritional abnormalities* *AND* The treatment must be given concomitantly with standard therapy for this condition.
Population criteria:	Patient must be 12 years of age or older.
Prescriber Instructions	*Patients receiving PBS-subsidised treatment with this drug must be registered in the Australian Cystic Fibrosis Database Registry. Treatment must not be given to a patient who has an acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease in the last 4 weeks prior to commencing this drug.* The authority application must be in writing and must include: (1) a completed authority prescription form; and (2) a completed Cystic Fibrosis Lumacaftor with Ivacaftor Authority Application Supporting Information Form; and (3) a signed patient acknowledgement; or an acknowledgement signed by a parent or authorised guardian, if applicable; and (4) a copy of the pathology report detailing the molecular testing for the patient being homozygous for the F508del mutation on the CFTR gene; and *(5) the result of a FEV1 measurement performed within a month prior to the date of application. Note: FEV1, must be measured in an accredited pulmonary function laboratory, with documented no acute infective exacerbation at the time FEV1 is measured; and* *(6) evidence that the patient has either chronic sinopulmonary disease or gastrointestinal and nutritional abnormalities; and* *(7) a copy of a current medication history* *(8) a copy of a sweat chloride result; and* *(9) height and weight measurements at the time of application; and* *(10) a baseline measurement of the number of days of CF-related hospitalisation (including hospital-in-the home) in the previous 12 months.*

Administrative Advice	*Special pricing arrangements apply* *No increase in the maximum number of repeats may be authorised.* *No increase in the maximum quantity or number of units may be authorised.* Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001

2.2 The pre-PBAC response (p2) noted that there was no consistent treatment effect modification across lung function subgroups from the pivotal trials and therefore proposed that patients with severe lung disease would benefit equally from treatment with lumacaftor/ivacaftor as those with FEV1>40%. The sponsor further noted that not including a criterion for FEV1 would be consistent with the current listing for ivacaftor.

3 Background

3.1 Lumacaftor/ivacaftor was registered by the TGA for the treatment of cystic fibrosis in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene on 8 March 2016.

3.2 A major submission for lumacaftor/ivacaftor was rejected at the March 2016 PBAC meeting on the basis of an unacceptably high and uncertain incremental cost-effectiveness ratio at the requested price, and uncertainty around the impact of lumacaftor/ivacaftor on long-term improvements in lung function and survival (paragraph 7.1, lumacaftor/ivacaftor March 2016 Public Summary Document (PSD)).

3.3 The following table provides a summary of the key differences between the March 2016 submission and this current minor resubmission, including PBAC comments on the March 2016 submission.

Table 1: Summary of the previous and current submissions

Component	March 2016 major submission	Current resubmission
Requested PBS listing	Treatment of cystic fibrosis in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene.	Same (with changes suggested by the Secretariat during the evaluation of the March 2016 submission)
Requested price	S100 HSD public hospital DPMQ (lumacaftor 200 mg + ivacaftor 125 mg, 112 tablets): $[redacted]	Same

Component	March 2016 major submission	Current resubmission
Main comparator	Best supportive care **PBAC Comment:** "…best supportive care was the appropriate comparator" (paragraph 7.4)	Same
Clinical evidence	Two head-to-head trials comparing lumacaftor/ivacaftor to placebo; Traffic (n=374) and Transport (n=376). Supportive evidence from one extension trial (Progress, n=516).	Same
Key effectiveness data	Absolute change in $ppFEV_1$ (pooled result): 2.81 (95% CI: 1.80, 3.82) **PBAC Comment:** "…it was uncertain whether this observed improvement in ppFEV1 [2.81%] represented a clinically significant difference, noting that this was considerably smaller than the improvement of 10.58% (95% CI: 8.57, 12.59) demonstrated for ivacaftor monotherapy." (paragraph 7.6)	Same
Key safety data	Subjects with any: • adverse event RR: 0.99 (95% CI: 0.96, 1.02) • serious adverse event RR: 0.61 (95% CI: 0.46, 0.80) • treatment related serious adverse event RR: 1.75 (95% CI: 0.75, 4.13). **PBAC Comment:** "…the frequency of most adverse events appeared to be comparable between lumacaftor/ivacaftor and placebo; however, hepatobiliary serious adverse events occurred in a greater proportion of lumacaftor/ivacaftor patients than in placebo patients." (paragraph 7.10)	Same
Clinical claim	The submission described lumacaftor/ivacaftor as superior in terms of comparative effectiveness and equivalent in terms of comparative safety over best supportive care. **PBAC Comment:** "The PBAC noted the improvement in exacerbations, weight gain, BMI, the hospitalisation rate and antibiotic use associated with treatment with lumacaftor/ivacaftor in the short term but considered that the impact of ivacaftor/lumacaftor on improvements in long-term lung function and survival was uncertain." (paragraph 6.23) "The PBAC considered that the claim of equivalent comparative safety was reasonable in the short term but noted the long term safety of lumacaftor/ivacaftor is unknown." (paragraph 6.24)	Same
Economic evaluation	Cost-utility model with cost/QALY of more than $200,000. **PBAC Comment:** "…the base case ICER of more than $200,000 per QALY was unacceptably high and likely underestimated." (paragraph 7.15)	Revised [redacted] to reflect the change in the start date of the economic analysis resulting in a cost/QALY of more than $200,000.
Number of patients	Less than 10,000 in Year 1 increasing to less than 10,000 in Year 5.	Same

Component	March 2016 major submission	Current resubmission
Estimated net cost to PBS	More than $100 million in Year 1 increasing to more than $100 million in Year 5 for a total of more than $100 million over the first 5 years of listing. **PBAC Comment:** "The PBAC noted the significant opportunity cost of listing lumacaftor/ivacaftor, particularly in the context of the uncertainty of the long-term improvements in lung function." (paragraph 7.16)	Same ([redacted] – see below).
Risk sharing arrangement and pay-for-performance	The submission stated that the sponsor is 'open to discussing the details of the requested listing and the final pricing arrangement'. No further detail was provided in the submission, the PSCR or the pre-PBAC response. **PBAC Comment:** "The PBAC recalled that it recommended ivacaftor for listing with an ICER of $105,000 - $200,000 per QALY, in conjunction with risk sharing and pay-for-performance arrangements (Ivacaftor PSD, March 2014). The PBAC considered that, given the more modest clinical benefit, the price of lumacaftor/ivacaftor was too high to result in acceptable cost-effectiveness, even if it was recommended in conjunction with similar Risk Sharing and Pay For Performance Arrangements." (paragraph 7.15)	[redacted] to the PBS (without co-payments deducted) over 5 years to more than $100 million. [redacted]
PBAC decision	Reject on the basis of "unacceptably high and uncertain incremental cost effectiveness ratio at the requested price, and uncertainty around the impact of lumacaftor/ivacaftor on long-term improvements in lung function and survival." (paragraph 7.1)	-

Note: paragraph references refer to the March 2016 lumacaftor/ivacaftor PSD.

Table 2: PBAC matters of concern in previous consideration

Matters of concern	How the resubmission addresses it
"…it was uncertain whether this observed improvement in $ppFEV_1$…represented a clinically significant difference, noting that this was considerably smaller than the improvement…demonstrated for ivacaftor monotherapy." (paragraph 7.6) "The PBAC noted the ACPM advice on the clinical significance of the small improvement in $ppFEV_1$ as a primary endpoint, and the validity of putting greater emphasis on secondary endpoints (p6) which stated, "both pivotal studies met the primary endpoint and secondary lung function end points were also met. However, the Quality of Life (QoL) endpoint [CFQ-R] was not met and the BMI endpoint was not met in Study 103. Importantly the exacerbation endpoint was met in both studies. The demonstrated benefit is modest at best, and given the lack of QoL improvement demonstrated, may not be clinically significant in some patients." (paragraph 7.9)	Not addressed
"…the extrapolation of short-term results to longer-term efficacy [beyond the 24 week trial and additional 24 week extension study] was uncertain." (paragraph 7.7)	Not addressed.
"…it was difficult to interpret the impact of the effect of lumacaftor/ivacaftor on reduction in pulmonary exacerbations independent of its effect on $ppFEV_1$ (paragraph 7.8). "…$ppFEV_1$ drives the frequency of exacerbations in the model. The PBAC considered this appeared inconsistent with the assertion in the pre-PBAC response that the impact of lumacaftor/ivacaftor on exacerbations was independent of its impact on $ppFEV_1$." (paragraph 7.13)	Not addressed
"…the long-term safety of lumacaftor/ivacaftor is unknown."(paragraph 7.10)	Not addressed
"The PBAC considered that, at the requested price, the requested listing for lumacaftor/ivacaftor was not sufficiently cost effective to enable PBAC recommendation for PBS listing." (paragraph 7.11)	The requested price is not revised in the resubmission. [redacted] to the PBS (without copayments deducted) over 5 years to more than $100 million. The sponsor indicated a willingness to discuss [redacted].
"…the model relies on the assumption that that the treatment effect is sustained beyond the 24 weeks of the Traffic and Transport trials (and a further 24 weeks from the extension trial, Progress) to the modelled life time horizon. As the PBAC considered that the extrapolation of short-term results in $ppFEV_1$ to mortality was highly uncertain, the inclusion of this assumption in the model was not considered reasonable. Furthermore, the PBAC considered that the assumption that patients in the treatment group could not decline in $ppFEV_1$ was implausible." (paragraph 7.12)	Not addressed

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

4 Clinical place for the proposed therapy

4.1 Cystic fibrosis is an autosomal recessive disease caused by mutations in the CFTR gene. Cystic fibrosis is a progressive multi-organ disease that primarily affects the pulmonary and digestive systems.

4.2 As per the March 2016 major submission, the minor resubmission proposed that lumacaftor/ivacaftor be administered in addition to current best supportive care in patients aged 12 years and older who are homozygous for the F508 deletion mutation CFTR gene.

5 Comparator

5.1 The PBAC previously accepted that best supportive care is the appropriate comparator (paragraph 7.4, March 2016 PSD). The comparator was unchanged in the minor submission.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item as it was a minor submission.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (507), health care professionals (3) and organisations (3) via the Consumer Comments facility on the PBS website. The PBAC also recalled the consumer comments received and considered at the March 2016 meeting in support of the major submission for lumacaftor/ivacaftor. The comments described a range of benefits of treatment with lumacaftor/ivacaftor including improvement or maintenance of lung function, reduction in chest infections and exacerbations, weight gain, fewer hospital visits, fewer medications to be consumed on a daily basis, slowing disease progression and enabling stability of lung function, improving quality of life and enabling greater participation in society (including less time off work and school for illness). The comments noted that a small improvement in quality of life made a large difference to the life of patients. The comments also noted that lumacaftor/ivacaftor is a treatment which targets the underlying genetic defect which causes cystic fibrosis, rather than merely treating the symptoms of the disease.

6.3 The PBAC noted the advice received from Cystic Fibrosis Australia, Cystic Fibrosis NSW and Cystic Fibrosis SA clarifying the likely use of lumacaftor/ivacaftor in clinical practice. The PBAC specifically noted the advice that lumacaftor/ivacaftor is a targeted therapy which may stabilise lung function, reduce hospitalisations and utilisation of other drugs, decrease morbidity and mortality and improve quality of life. The PBAC noted that this advice was supportive of the evidence provided in the submission.

Clinical trials

6.4 No new clinical trials were presented in the resubmission. The March 2016 major submission was based on two head-to-head trials comparing lumacaftor/ivacaftor to

placebo; Traffic (n=374) and Transport (n=374). Supportive evidence from one extension trial (Progress, n=516) was also presented.

Comparative effectiveness

6.5 The minor resubmission represented the results from the TRAFFIC and TRANSPORT trials. In March 2016 "the PBAC noted that, based on two head-to-head trials comparing lumacaftor/ivacaftor to placebo, lumacaftor/ivacaftor resulted in a 2.81% (95% CI: 1.80, 3.82) increase in absolute per cent predicted forced expiratory volume in one second ($ppFEV_1$) over a median duration of follow-up of 24 weeks. The PBAC agreed with ESC that it was uncertain whether this observed improvement in $ppFEV_1$ represented a clinically significant difference, noting that this was considerably smaller than the improvement of 10.58% (95% CI: 8.57, 12.59) demonstrated for ivacaftor monotherapy" (paragraph 7.6, March 2016 PSD). Table 3 from the March 2016 PSD is included below.

Table 3: Results of absolute change in $ppFEV_1$ in the direct randomised trials

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

Source: Table B.6.1, p 93 of the submission
Abbreviations: SE, standard error; CI, confidence interval; q12h, every 12 hours; qd, daily.
^Least squares mean difference

6.6 In its consideration of the March 2016 major submission, the ESC considered the incremental improvements (compared with placebo) demonstrated in patient's weight, $ppFEV_1$ and CFQ-R were more compelling for ivacaftor monotherapy than for lumacaftor/ivacaftor (see the below table)" (paragraph 7.6, March 2016 PSD).

Table 4: Selected comparison of incremental improvements (compared with placebo) for lumacaftor/ivacaftor (in F508del/F508del) and ivacaftor (in G551D)

Outcome	Lumacaftor/ivacaftor LSMD (95% CI)	Ivacaftor LSMD (95% CI)
$ppFEV_1$: Absolute difference from baseline at 24 weeks	2.81 (1.80, 3.82)	10.58 (8.57, 12.59)
Weight: Absolute difference from baseline in weight-for-age z-score at week 24	0.0678 (0.0256, 0.1100)	0.319 (0.146, 0.492)
CFQ-R: Absolute difference from baseline in CFQ-R Respiratory Domain Score at Week 24	2.22 (-0.01, 4.45)	7.06 (3.66, 10.46)*

Source: March 2016 lumacaftor with ivacaftor PSD
LSMD = least squares mean difference.
*Result for adolescents and adults – subjects 14 years and older. Pooled result for adolescents/adults and children was 8.08 (4.73, 11.42).

6.7 In March 2016, the PBAC noted the statistically significant improvements in the number of pulmonary exacerbations but considered that "it was difficult to interpret the impact of the effect of lumacaftor/ivacaftor on reduction in pulmonary exacerbations independent of its effect on $ppFEV_1$" (paragraph 7.8, March 2016 PSD).

6.8 The minor resubmission presented updated outcomes data for ivacaftor in the G551D population and stated that these data demonstrate that the improvements in intermediate outcomes observed in the pivotal ivacaftor trials (STRIVE and ENVISION) translated to substantial improvements in long-term, highly-patient relevant outcomes. The relevance of this finding to lumacaftor/ivacaftor was unclear.

Clinical claim

6.9 The minor resubmission claimed superior comparative effectiveness, in terms of improvements in lung function as measured by $ppFEV_1$, rate of pulmonary exacerbations and nutritional status, and that these outcomes are associated prolongation of life. The minor resubmission did not state a claim regarding comparative safety; however the previous major submission claimed equivalent comparative safety with best supportive care.

6.10 In March 2016, "the PBAC noted the improvement in exacerbations, weight gain, BMI, the hospitalisation rate and antibiotic use associated with treatment with lumacaftor/ivacaftor in the short term but considered that the impact of ivacaftor with lumacaftor on improvements in long-term lung function and survival was uncertain". In addition, "the PBAC considered that the claim of equivalent comparative safety was reasonable in the short term but noted the long term safety of lumacaftor/ivacaftor is unknown." The minor resubmission did not address these concerns.

Economic analysis

6.11 The March 2016 major submission presented a cost-utility analysis compared with best supportive care. The minor resubmission made two revisions to that model:

- The minor resubmission changed the assumed date of PBS listing of lumacaftor/ivacaftor. The model included an assumption that the price of lumacaftor/ivacaftor would [redacted] The Secretariat assumed that the minor resubmission changed the date of PBS listing from 1 July 2016 to 1 March 2017, which reduced the time listed on the PBS until loss of exclusivity from [redacted] to [redacted] years (Step 3 in Table 5).
- The minor resubmission stated that the model was revised to [redacted] to the PBS of lumacaftor/ivacaftor treatment at more than $100 million over 5 years. The Secretariat replicated the revised ICER of more than $200,000 per QALY using an effective DPMQ of $[redacted] (Step 4).

Table 5: Results of the stepped economic evaluation

Step and component	BSC	Lumacaftor/ivacaftor	Increment
Step 1: 24-week time-horizon			
Costs	$18,712	$	$
QALYs	0.322		
Incremental cost/extra QALY gained			$
Step 2: life-time time horizon (March 2016 major submission base case)			
Costs	$380,017	$	$
QALYs	4.894		
Incremental cost/extra QALY gained			$
Step 3: initiation of PBS reimbursement date changed to 1 March 2017			
Costs	$380,017	$	$
QALYs	4.894		
Incremental cost/extra QALY gained			$
Step 4: financial cap, replicated using assumed effective DPMQ of $ (November 2016 minor resubmission base case)			
Costs	$380,017	$	$
QALYs	4.894		
Incremental cost/extra QALY gained			$

Source: Table D.5.5, p 166 of the March 2016 major submission, p 5 of the November 2016 minor submission and calculated during the preparation of the minor overview using the March 2016 economic model.

6.12 The redacted table above shows an ICER of more than $200,000 per QALY. The minor resubmission stated that when discounting was removed, the ICER reduced to $105,000 - $200,000 per QALY; this was verified by the Secretariat. The sponsor requested that the PBAC consider the cost effectiveness of lumacaftor/ivacaftor using a lower discount rate given the young age of the cystic fibrosis population and the chronic nature of the disease, where benefits in terms of life years gained accrue far into the future. The base case ICER in the March 2014 ivacaftor submission was calculated using a 5% discount rate for costs and outcomes.

6.13 In March 2016, the PBAC considered that the estimated cost per QALY gained for lumacaftor/ivacaftor compared with best supportive care was likely to be underestimated (paragraphs 7.12-7.14, March 2016 PSD). The minor resubmission did not address the following concerns raised by the PBAC:

- The model relied on the assumption that the treatment effect is sustained beyond the 24 weeks of the Traffic and Transport trials (and a further 24 weeks from the extension trial, Progress) to the modelled life-time time horizon. As the PBAC considered that the extrapolation of short-term results in $ppFEV_1$ to mortality was highly uncertain, the inclusion of this assumption in the model was not considered reasonable. Furthermore, the assumption that patients in the treatment group could not decline in $ppFEV_1$ was considered implausible.
- $ppFEV_1$ drives the frequency of exacerbations in the model which appeared inconsistent with the assertion in the March 2016 pre-PBAC response that the impact of lumacaftor/ivacaftor on exacerbations was independent of its impact on $ppFEV_1$. Similarly, in March 2016 the PBAC did not accept the additional contribution of pulmonary exacerbations on mortality, independent of effect on FEV_1.

[redacted]

6.14 In March 2016, in addition to considering that the base case ICER was likely underestimated, the PBAC considered that it was already unacceptably high, at more than $200,000 per QALY. The PBAC recalled that it recommended ivacaftor [for the G551D population] for listing with an ICER of $105,000 - $200,000 per QALY, in conjunction with risk sharing and pay-for-performance arrangements (Ivacaftor PSD, March 2014). The PBAC considered that, given the more modest clinical benefit [with lumacaftor/ivacaftor versus placebo compared with ivacaftor versus placebo], the price of lumacaftor/ivacaftor was too high to result in acceptable cost-effectiveness, [redacted]" (paragraph 7.15, March 2016 PSD).

Drug cost/patient/year: $[redacted]

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

Estimated PBS usage & financial implications

6.16 The estimated utilisation and financial implications were unchanged from the March 2016 major submission, [redacted](see the following section). At year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS [redacted] would be more than $100 million. The estimated net cost to government health budgets over the first five years of listing [redacted] was estimated to be more than $100 million.

Table 6: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Estimated extent of use						
Number treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Uptake rate	100%	100%	100%	100%	100%	-
Packs[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS/RPBS						
Gross cost to PBS/RPBS[b]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Gross cost to PBS/RPBS – including proposed cap[c]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/RPBS – including proposed cap	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated net cost to other government budgets						
Net cost to non-PBS services	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Estimated total net cost						
Net cost to government health budgets – without cap	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**
Net cost to government health budgets – including proposed cap	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**

Source: Table E.2.7, p174 and Table E.4.2, p 178 of the March 2016 major submission and Table 1 of the November 2016 minor resubmission.

[a] Assuming 11 packs per year as estimated by the submission.

[b] Without co-payment deducted.

[c] Yearly costs calculated by the Secretariat using an assumed effective DPMQ of $[redacted].

6.17 The pre-PBAC response (p2) noted that, as of 26 September 2016, there were 96 patients receiving treatment with lumacaftor/ivacaftor under a compassionate use program. The sponsor did not clarify whether these patients were included in the estimated patient numbers.

Financial Management – Risk Sharing Arrangements

6.18 The minor resubmission [redacted] to the PBS/RPBS (i.e. without the co-payment deducted) over the first five years of PBS listing to more than $100 million (see Table 8).

6.19 In addition, the minor resubmission noted that the sponsor would be willing to work with the PBAC and the Department of Health [redacted]

6.20 The pre-PBAC response (p1) noted that lumacaftor/ivacaftor is funded for all eligible patients in France and Germany while negotiations on price are ongoing. It is also fully reimbursed for all eligible patients in Austria and Luxemburg and available through individual funding requests without restrictions for patients in Norway, Italy, Denmark and Israel (with assessment and/or negotiations ongoing in Norway, Denmark and Italy). The sponsor did not provide any information regarding the circumstances through which lumacaftor/ivacaftor is reimbursed in these countries.

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

7 PBAC Outcome

7.1 Lumacaftor with ivacaftor was not recommended by the PBAC on the basis of unfavourable and uncertain cost-effectiveness at the requested price. The PBAC noted that the resubmission did not address the issues it previously identified in its consideration of the March 2016 submission (see Table 2). The PBAC particularly noted the continuing uncertainty regarding long-term benefits of treatment on lung function and overall survival.

7.2 As per its previous consideration, the PBAC recognised the potential clinical value of lumacaftor/ivacaftor in the treatment of cystic fibrosis in patients aged 12 years or older who are homozygous for the F508del mutation. The PBAC acknowledged the many consumer comments received relating to this submission, as well as the March 2016 major submission. The PBAC also acknowledged the correspondence from Cystic Fibrosis Australia, Cystic Fibrosis NSW and Cystic Fibrosis SA for this submission. The PBAC recognised the strong support for subsidised access to lumacaftor/ivacaftor.

7.3 The PBAC noted that the only change made in the minor resubmission was [redacted] over the first five years of listing. The resubmission presented a revised ICER based on an effective price for lumacaftor/ivacaftor which took into account the difference in the estimated financial implications [redacted]. While [redacted], the PBAC noted that this approach did not provide a stable estimate of cost-effectiveness. In addition, the model assumed that the [redacted] The PBAC considered this assumption was inappropriate as the [redacted] for the first five years of listing. In any case, the PBAC considered that the ICER of more than $200,000 per QALY was unacceptably high and was likely underestimated due to the issues outlined in paragraph 6.13.

7.4 The pre-PBAC response noted that the ICERs for both ivacaftor and lumacaftor/ivacaftor are strongly driven by discounting and that a lower discount rate could be considered as a means of prioritising improvements in outcomes in this young patient population with cystic fibrosis. The PBAC noted its preference for a discount rate of 5% per annum for both costs and outcomes. In this regard, the PBAC recalled that it recommended ivacaftor for listing with an ICER of $105,000 - $200,000 per QALY, in conjunction with risk sharing and pay-for-performance

arrangements (ivacaftor PBAC PSD, March 2014) and that this ICER was calculated using the 5% discount rate for costs and outcomes. The PBAC reiterated that the recommendation for ivacaftor set a precedent for acceptable cost-effectiveness, in this setting.

7.5 The PBAC noted that the net cost of lumacaftor/ivacaftor to government over the first five years of listing [redacted] was estimated to be more than $100 million, with less than 10,000 patients treated in year 5.

7.6 The PBAC noted that the F508del/F508del population is around four times larger than the G551D population who are eligible for ivacaftor monotherapy. Accordingly, the PBAC considered that [redacted] than that for ivacaftor to manage the uncertainty regarding long-term benefits of treatment on lung function and overall survival.

7.7 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

8 Context for Decision

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

9 Sponsor's Comment

The sponsor had no comment.