

6.05 IVACAFTOR,

Sachet containing granules 50 mg, 75 mg, Kalydeco[®], Vertex Pharmaceuticals Pty Ltd.

1 Purpose of Application

- 1.1 The submission requested a Section 100 (Highly Specialised Drugs Program), Authority Required listing for ivacaftor granules for treatment of cystic fibrosis (CF) in patients aged 12 to 24 months who have a G551D mutation or other class III gating mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.
- 1.2 Ivacaftor is currently subsidised by the PBS for the treatment of patients aged 2 years and older who have a G551D mutation or other class III gating mutation in the CFTR gene.

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

Component	Description
Population	12–24-month old cystic fibrosis patients with a confirmed class III gating mutation on at least one allele of the CFTR gene.
Intervention	Ivacaftor.
Comparator	Best supportive care.
Outcomes	Primary outcome: <ul style="list-style-type: none"> • Mean ivacaftor, M1-ivacaftor, and M6-ivacaftor plasma concentrations Secondary and tertiary outcomes: <ul style="list-style-type: none"> • Absolute change from baseline in nutritional status (weight, length, weight-for-length z-scores, weight-for-length-for-age z-scores, and weight-for-length percentiles). • Absolute change from baseline in sweat chloride. • Absolute change from baseline in LCI. • Absolute change from baseline in faecal elastase-1 (FE-1). • Absolute change from baseline in IRT. • Measures of pulmonary exacerbations (PEX).
Clinical claim	Ivacaftor plus BSC is superior in terms of effectiveness compared with BSC alone Ivacaftor plus BSC is non-inferior in terms of safety compared to BSC alone

Abbreviations: BSC=best supportive care; CFTR=cystic fibrosis transmembrane conductance regulator; FE=faecal elastase; IRT=immunoreactive trypsinogen; LCI=lung clearance index; PEX=pulmonary exacerbations.

Source: Table 1.1.1, p8 of the submission

2 Requested listing

- 2.1 A summary of the proposed listing details is provided in Table 2.

Table 2: Details of the proposed listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
Ivacaftor, 50 mg granules, 4 x 14 sachets	1	56	5	\$22,500.00	Kalydeco [®] , Vertex Pharmaceuticals
Ivacaftor, 75 mg granules, 4 x 14 sachets	1	56	5	\$22,500.00	

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Episodicity:	<i>Chronic</i>
Severity:	<i>N/A</i>
Condition:	Treatment of cystic fibrosis in patients aged ≥ 12 months and older who have a G551D or other gating (class III) mutation in the CFTR gene.
PBS Indication:	Treatment of cystic fibrosis in patients 12 to 24 months old who have a G551D or other gating (class III) mutation in the CFTR gene on at least one allele.
Treatment phase:	Initial
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing
Treatment criteria:	Patient must not receive more than 24 weeks of treatment under this restriction, AND The treatment must be given concomitantly with standard therapy for this condition.
Clinical criteria:	Patients must be assessed through a cystic fibrosis clinic/Centre which is under the control of specialist respiratory physicians with experience and expertise in the management of cystic fibrosis. If attendance at such a unit is not possible because of geographical isolation, management (including prescribing) may be in consultation with such a unit, AND Patient must have G551D mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene on at least 1 allele; OR Patient must have other gating (class III) mutation in the CFTR gene on at least 1 allele, AND
Population criteria:	Patients must be aged ≥ 12 months
Prescriber Instructions:	The authority application must be in writing and must include: (1) a completed authority prescription form; and (2) a completed Cystic Fibrosis Ivacaftor Authority Continuing Application Supporting Information Form; and (3) the result of a FEV ₁ measurement performed within one month prior to the date of application, if aged 6 years or older. Note: FEV ₁ , must be measured in an accredited pulmonary function laboratory, with documented no acute infective exacerbation at the time FEV ₁ is measured; and (4) a copy of a current medication history, including any CYP3A4 inhibitors and/or CYP3A4 inducers; and (5) height and weight measurements at the time of application; and (6) a measurement of number of days of CF-related hospitalisation (including hospital in the home) in the previous 6 months.

Abbreviations: CF=cystic fibrosis; CFTR=cystic fibrosis transmembrane conductance regulator; FEV₁=forced expiratory volume in one second; N/A=not applicable; PBS=Pharmaceutical Benefits Scheme

Source: Table 1.4.2, p29 of the submission.

- 2.2 The proposed restriction as summarised is consistent with the TGA indication. The proposed restriction criteria, pack size and repeats were appropriate and consistent with criteria currently applied to ivacaftor in patients aged 2 years and older.
- 2.3 Each dose of ivacaftor granules (50 mg and 75 mg) should be mixed with one teaspoon (5 mL) of applesauce or other appropriate food for administration. Administration of ivacaftor granules mixed with food presents a wastage risk in very young children (potentially through regurgitation of the ivacaftor mixed with food, or refusal to eat, and drug stability of only one hour when mixed). This may affect the cost-effectiveness of ivacaftor in clinical practice in this setting. The submission did not present an economic evaluation.
- 2.4 Although the submission did not present an economic evaluation, the requested basis for listing is the same as that presented in the submission for the ivacaftor granules

(50 mg and 75 mg) for treatment of CF in patients who have a G551D mutation or other class III gating mutations in the CFTR gene in patients aged 2 to 5 years. In the 2 to 5 year age group submission, cost-effectiveness was assessed compared with best supportive care (BSC), as would apply for the current submission (12 to 24 months). (Ivacaftor, Public Summary Document (PSD) November 2016, paragraph 6.23).

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:** The TGA delegate's file note was available. The TGA delegate's file note states that the delegate "has no concerns with approving the submission for registration. However, the long term benefits of treatment and relative benefits of treating at a younger age are unknown".

The TGA Clinical Evaluation Report Round 1 was available. The submission for monotherapy with ivacaftor granules was made under the TGA/PBAC Parallel Process. The TGA CER (p27) concluded the claim made by the sponsor that early intervention in CF will improve long term outcomes is not very convincing and difficult to establish based on the available evidence (a small open label study in which efficacy was a tertiary and exploratory endpoint). The CER noted there was a small improvement in nutritional status, an important marker of disease activity. The CER stated that the lack of a long-term randomised trial needs to be balanced against the challenges (including ethics) of performing one.

Previous PBAC consideration

- 3.2 Monotherapy with ivacaftor 50 mg and 75 mg granules for the treatment of CF patients aged 2 to 5 years that have a G551D mutation or other gating (class III) mutation in the CFTR gene has been considered by the PBAC on previous occasions. An application for listing was deferred in November 2016 on the basis of uncertain cost effectiveness and that further negotiation was required to ensure that the submission's intent of the proposed listing having no net financial impact could be achieved in practice (Ivacaftor, PSD November 2016, paragraph 7.1).
- 3.3 The PBAC considered that the intention of the submission [REDACTED] was appropriate, 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 this could be achieved in practice through the existing risk sharing arrangement and patient caps. 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 PSD November 2016, paragraph 7.7).

3.4 At the January 2017 meeting ivacaftor was recommended for the treatment of patients aged 2 to 5 years based on the following:

- Updated data from the Ivacaftor Long Term Safety Study from the US CF registry which indicated a benefit in terms of: a reduction in the risk of hospitalisation and pulmonary exacerbations (PE_x) in patients aged <6 years who were treated with ivacaftor compared with matched controls (RR 0.68, 95%CI: 0.49-0.95).
- An additional post hoc analysis from the ENVISION RCT (patients 6 years of age and older) for change from baseline in FEV₁ which supported the conclusion that the efficacy of ivacaftor is independent of age. (Ivacaftor, Addendum PSD November 2016, p18).
- Updated cost-effectiveness analyses which suggested the cost per quality adjusted life year (QALY) was similar for the cohort aged 2-5 years (\$105,000/QALY - \$200,000/QALY) and the cohort aged 6+ years \$105,000/QALY - \$200,000/QALY” (Ivacaftor, PSD November 2016, p18).

The PBAC also recommended that, as proposed by the sponsor, [REDACTED] in the current ivacaftor risk share arrangement, and that [REDACTED] (Ivacaftor, Addendum November 2016, p18).

3.5 At that same meeting (January 2017), the PBAC reiterated its advice that the cost per patient should be no higher if a patient over 25 kg chooses to use the ivacaftor granules, compared to the cost of treatment with the ivacaftor tablets (Ivacaftor, Addendum PSD November 2016, p18).

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

4 Population and disease

4.1 Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations in the CFTR gene. It is a progressive multi-organ disease that primarily affects the pulmonary and digestive systems. Ivacaftor is currently subsidised by the PBS for the treatment of patients aged 2 years and older who have a gating (class III) mutation in the CFTR gene. The current submission sought an extension of the PBS listing to include paediatric patients aged 12–24 months old with gating (class III) mutations in the CFTR gene.

4.2 The submission proposed that ivacaftor will be administered as an add-on to BSC.

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

5 Comparator

5.1 The submission nominated best supportive care (BSC) as the main comparator. This was appropriate and was consistent with the approach used in previous submissions in this indication for older age groups.

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 (50), a health care professional (1) and Cystic Fibrosis Australia via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with ivacaftor including reduction in hospital admissions, improvement in lung function and improvement in quality of life. The comments also emphasised the potential benefits of starting treatment with ivacaftor as early as possible.

6.3 Cystic Fibrosis Australia indicated support for ivacaftor granules to be listed on the PBS for patients aged 12 to 24 months emphasising the importance for patients to receive treatment early.

Clinical trials

6.4 The submission was based on one 24-week open label trial evaluating the safety and efficacy of ivacaftor granules 50 mg and 75 mg (Study 124 (Part A (N=7); Part B (N=19))). There were no head-to-head randomised trials available comparing ivacaftor plus BSC with BSC.

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

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Trials meeting the selection criteria: Study VX15-770-124 (Study 124)	A phase III, 2-part, open label, non-randomised, multicentre study to evaluate the safety, pharmacokinetics and pharmacodynamics of ivacaftor in subjects with cystic fibrosis who are less than 24 months of age at treatment initiation and have a CFTR gating mutation.	February 2015
	Rosenfeld, M.; Wainwright, C. E.; Higgins, M.; Wang, L. T.; McKee, C.; Campbell, D.; Tian, S.; Schneider, J.; Cunningham, S.; Davies, J. C.; Harris, W.; Mogayzel, P.; McCoy, K.; Milla, C.; Rubenstein, R.; Walker, S.; Black, P.; Montgomery, G.; McColley, S.; Hiatt, P.; Sawicki, G.; Rock, M.; Aurora, P.; Ratjen, F.; Maitra, A.; Ives, A.; Gaillard, E.; McNalley, P.; Selvadurai, H.; Robinson, P. Ivacaftor treatment of cystic fibrosis in children aged 12 to <24 months and with a CFTR gating mutation (ARRIVAL): a phase 3 single-arm study.	The Lancet Respiratory Medicine. 2018; 6(7):545-553
	Rosenfeld, M.; Wainwright, C.; McKee, C.; Higgins, M.; Wang, L.; Campbell, D.; Tian, S.; Schneider, J.; Cunningham, S.; Davies, J. C. A phase 3, 2-part, single-arm study of ivacaftor treatment in patients <2 years with a CFTR gating mutation: results from the ARRIVAL study in patients 1 to 2 years.	Journal of Cystic Fibrosis. 2018; 17(Supplement 3): S1
	Vertex Pharmaceuticals Incorporated. A Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Ivacaftor in Subjects With Cystic Fibrosis Who Are Less Than 24 Months of Age and Have a CFTR Gating Mutation	2016 https://ClinicalTrials.gov/show/NCT02725567
	Vertex Pharmaceuticals Incorporated. A study to assess the safety, pharmacokinetics, and pharmacodynamics of ivacaftor in children less than 24 months of age with cystic fibrosis (a rare hereditary disease that affects the lungs, digestive system and other organs)	2016. EUCTR2015-001997-16-GB
Trials excluded from analysis: Study 126	A Phase 3, 2-Arm, Open-label Study to Evaluate the Safety and Pharmacodynamics of Long-term Ivacaftor Treatment in Subjects With Cystic Fibrosis Who Are Less Than 24 Months of Age at Treatment Initiation and Have an Approved Ivacaftor-Responsive Mutation.	2017

Abbreviations: CFTR= cystic fibrosis transmembrane conductance regulator.

Source: Table 2.2.1, p35 of the submission.

6.6 The submission excluded Study 126 from analysis, as it was ongoing. This was appropriate.

6.7 The key features of the included evidence are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Ivacaftor + BSC					
Study 124	Part A (N=7) Part B (N=19)	OL, MC, single arm, 2-part study Part A: 4 days Part B: 24 weeks	High	Aged 12 to 24 months with CF with a CFTR gating mutation on at least one allele.	Absolute change from baseline in sweat chloride concentration, pancreatic function (FE-1, IRT), nutritional status (length and weight), pulmonary exacerbations (PEX) and CF-related hospitalisations

Abbreviations: CF=cystic fibrosis; CFTR=CF transmembrane conductance regulator gene; FE=faecal elastase; IRT= immunoreactive trypsinogen; MC=multi-centre; OL=open label; PEX=pulmonary exacerbations; ppFEV₁=percent predicted forced expiratory volume in 1 second.

Source: Compiled during the evaluation.

- 6.8 Only Part B of Study 124 assessed efficacy outcomes to 24 weeks (Part A reported on safety and pharmacokinetic outcomes only).
- 6.9 The following issues were identified with regards to the study design, analysis and its implications:
- Study 124 was a non-randomised, single-arm, open label trial. The study was designed to demonstrate the safety, pharmacokinetics and pharmacodynamics of ivacaftor in children aged 12 to 24 months. The overall risk of bias for the trials was high due to its non-randomised and open-label nature. However, the key efficacy outcomes are objective measures, and sweat chloride, pancreatic function (FE-1, IRT), weight, stature (length) were based on objective laboratory analyses. Safety was the primary outcome for Study 124, and the safety populations were used as the basis of analysis.
 - The sample size was small and results are only available up to 24 weeks.
 - The absence of a comparator group means it is not possible to assess the comparative safety/efficacy outcomes for ivacaftor in this patient group.
 - The Pre-Sub-Committee Response (PSCR) stated that due to the young age of the study population, the small number of available patients and withholding a known effective treatment in the study of young children, conducting a randomised controlled trial was deemed inappropriate. The ESC acknowledged the difficulties in obtaining randomised controlled trial data for this patient population.

Comparative effectiveness

- 6.10 Study 124 did not include outcomes for ppFEV₁ (percent predicted forced expiratory volume in 1 second). The submission noted that this was due to the difficulty of assessing ppFEV₁ in this young cohort. The evaluation considered this was reasonable. The use of the lung-clearance index (LCI) as a measure of the impact of treatment on lung function was proposed. However, results for the change in LCI were available for one patient only in Study 124. The available results from Study 124 showed treatment with ivacaftor resulted in an improvement from baseline in the following outcomes (see Table 7):
- Mean absolute improvement in sweat chloride of -73.5 (SD=17.5, p=NR) mmol/L at 24 weeks. The ESC noted that the mean improvement in sweat chloride exceeded the improvement in sweat chloride demonstrated in older patients treated with ivacaftor in the KIWI (2-5 years), ENVISION (≥6 years) and STRIVE (≥6 years) trials. Further, the ESC noted that the mean sweat chloride at Week 24 (33.8 mmol/L) approaches the threshold of ≤30 mmol/L which is the diagnostic cut-off for normal sweat chloride in this patient population (Study 124 Clinical Study Report, p8).
 - The mean absolute improvement from baseline to Week 24 in FE-1 concentration of 164.7 µg/g (SD=151.9, p=NR).

- Reductions in IRT concentration were seen by Week 2 and sustained to Week 24; a 56% mean improvement from baseline to Week 24 of -647.1 ng/mL (SD=339.3, p=NR).
 - Mean weight was increased at each time point to Week 24 from 10.5 kg (SD=1.3) at baseline to 12.0 kg (SD=1.4). The mean absolute change in weight from baseline at Week 24 was 1.4 kg (SD=0.6). Mean weight-for-age z-score was generally sustained or increased at each time point to Week 24 from 0.31 (SD=0.74, p=NR) at baseline to 0.48 (SD=0.83).
 - Mean length was increased at each time point to Week 24 from 78.0 cm (SD=3.7) at baseline to 84.3 cm (SD=4.0). Mean length-for-age z-score was generally sustained at each time point to Week 24 from -0.30 (SD 0.82, p=NR) at baseline to 0.03 (SD 0.91).
 - Mean weight-for-length percentile was increased or sustained at each time point to Week 24 from 68.2% (SD=6.0) at baseline to 69.9% (SD=17.1). Mean weight-for-length-for-age z-score at baseline (0.61%, SD=0.90) was generally sustained at Week 24 (0.69%, SD=0.98, p=NR).
 - The submission used two definitions for analysis of PEx due to the absence of a consensus definition for this patient group. Eight patients (42.1%) had a total of 13 PEx as defined by Definition 1 (event rate/year = 1.55), or five subjects (26.3) had a total of eight PEx according to Definition 2 (event rate/year = 0.95).
- 6.11 The ESC considered that intermediate outcomes from Study 124 which demonstrated an increase in patient weight could indicate benefit in early treatment as patients in this age group often have difficulty with weight gain. However, the ESC considered there was uncertainty in interpreting these results given open label design, short duration and small sample size of Study 124. The ESC noted the magnitude of the increase from baseline of weight-for-age z-score and stature-for-age z-score were generally comparable across Study 124 and KIWI/KLIMB trials.

Comparative harms

- 6.12 The submission reported no deaths, no serious adverse events (SAEs), no AEs that led to permanent treatment discontinuation, and no AEs that led to treatment interruption in participants aged 12 to <24 months in in Part A. The submission reported no deaths in participants aged 12 to <24 months in Part B of the study. The submission reported 18 of the 19 patients in Part B experienced AEs. A summary of the key adverse events for ivacaftor from Part B of Study 124 is presented in Table 5.

Table 5: Summary of key adverse events in Study 124 occurring in at least two subjects by system organ class and preferred term, Safety set, Part B (participants aged 12 to <24 months)

System Organ Class ^a Preferred Term	Ivacaftor 50 mg N=19 n (%)
Patients with any AEs	18 (94.7)
Respiratory, thoracic, and mediastinal disorders	16 (84.2)
Cough	14 (73.7)
Rhinorrhoea	6 (31.6)
Infections and infestations	10 (52.6)
Otitis media	4 (21.1)
Upper respiratory tract infection	4 (21.1)
Conjunctivitis	2 (10.5)
Rhinitis	2 (10.5)
Investigations	10 (52.6)
Aspartate transaminase increased	7 (36.8)
Alanine transaminase increased	6 (31.6)
Blood pressure increased	3 (15.8)
Gamma-glutamyltransferase increased	3 (15.8)
Pseudomonas test positive	3 (15.8)
Blood lactate dehydrogenase increased	2 (10.5)
General disorders and administration site conditions	7 (36.8)
Pyrexia	7 (36.8)
Gastrointestinal disorders	6 (31.6)
Constipation	3 (15.8)
Vomiting	3 (15.8)
Metabolism and nutrition disorders	2 (10.5)
Dehydration	2 (10.5)

Abbreviations: AE=adverse event; IVA=ivacaftor; n=size of subsample; N=total sample size; SOC=System Organ Class; PT=Preferred Term

Note: ^a A patient with multiple events within a category (Any, SOC, or PT) was counted only once in that category.

Source: Table 2.5.17, p71 of the submission

Benefits/harms

6.13 Study 124 was a single-arm study. As such, it was not possible to present a comparative benefit-to-harms summary.

Clinical claim

6.14 The submission described ivacaftor plus BSC as superior in terms of effectiveness compared with BSC alone and non-inferior in terms of safety compared with BSC alone. Given the absence of a comparator group and the small patient numbers in Study 124, the therapeutic conclusion presented was not adequately supported by the evidence presented in the submission.

6.15 The submission assumed ivacaftor plus BSC is similar in terms of comparative effectiveness and safety in patients aged from 12 to <24 months compared with patients aged 2 years and older.

6.16 The PBAC has previously considered ppFEV₁ as the outcome of interest in CF patients aged ≥ 2 years. In the absence of that outcome in this patient cohort, the evaluation presented a frame of reference comparison (Table 7) of the results available in Study 124 with comparable results from previous studies in older age groups in the same

indication. Comparison of those data suggests that changes in sweat chloride and morphometric measures for patients in Study 124 were consistent (within the bounds of the reported SD) with those for patients in older age groups (aged 2-5 years or 6 years and older). However, there were slightly more PEx in patients aged 12 to <24 months than in older age groups.

Table 6: Comparison of efficacy outcomes for ivacaftor across trials

Age group	2 to <24 months	2 – 5 years				≥ 6 years			
Study ID	Study 124	KIWI		KLIMB		ENVISION/ PERSIST		STRIVE/ PERSIST	
Mean Δ (SD) from baseline	24 wks	24 wks		108 wks ^a		24 wks	144 wks ^b	24 wks	144 wks ^b
	50 mg N=19	50 mg N=10	75 mg N=24	50 mg N=9	75 mg N=24	150 mg N=52	150 mg N=25	150 mg N=161	150 mg N=72
ppFEV ₁ (% points)	NR	-12.5 (30.12)	4.3 (14.78)	3.8 (18.1)	13.8 (20.0)	10.67	10.30 (12.4)	10.13	9.40 (10.8)
Sweat chloride (mmol/L)	-73.5 (17.5)	-47.1 (24.26)	-46.8 (27.58)	-46.5 (31.0)	-58.1 (23.9)	-58.6	NR	-52.2	NR
BMI-for-age z-score (units)	0.07 (0.65)	0.46 (0.456)	0.34 (0.417)	0.40 (0.77)	0.21 (0.59)	0.33	NR	0.36	NR
BMI (kg/m ²)	NR	0.33 (0.539)	0.31 (0.549)	-0.16 (0.96)	0.28 (0.97)	0.28	2.5 (1.6)	0.91	1.2 (2.2)
Weight-for-age z-score (units)	0.15 (0.42)	0.18 (0.317)	0.21 (0.228)	0.16 (0.78)	0.21 (0.55)	0.30	NR	0.33	NR
Weight (kg)	1.4 (0.60)	1.0 (0.42)	1.5 (0.55)	4.0 (1.2)	5.7 (1.9)	3.69	14.8 (5.7)	3.11	4.1 (7.1)
Stature-for-age z-score (units)	0.28 (0.60)	-0.25 (0.448)	0.08 (0.216)	-0.14 (0.41)	0.24 (0.40)	NR	NR	NR	NR
Stature (cm)	6.1 (1.6)	2.5 (1.45)	3.5 (0.93)	13.6 (2.3)	15.0 (2.3)	NR	NR	NR	NR
Pulmonary exacerbations - no. events (observed events per patient per year) Definition 1 ^a	13 (1.55)	5 (0.54)	30 (1.24)	17 (1.75)	23 (0.97)	NR	NR	NR	NR
Pulmonary exacerbations (no. events (event rate) Definition 2 ^a	8 (0.95)	2 (0.21)	4 (0.17)	4 (0.41)	5 (0.21)	NR	NR	NR	NR

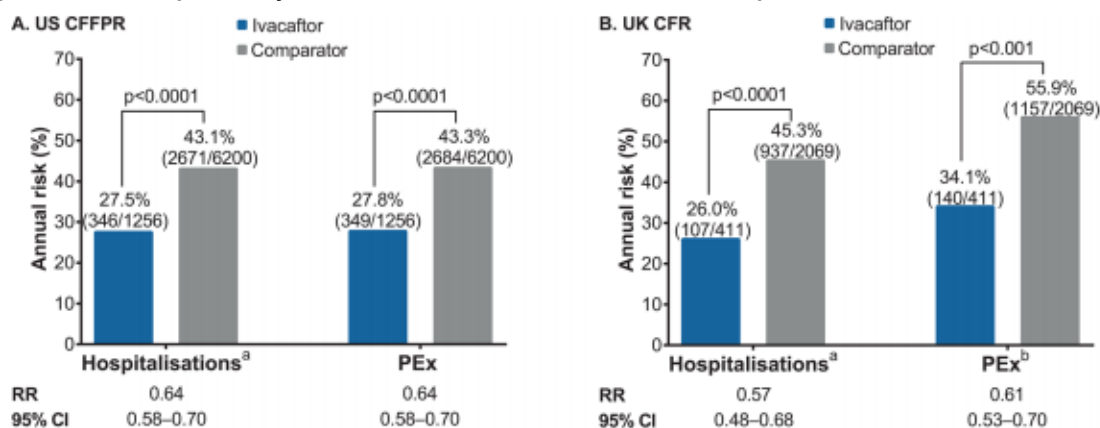
Abbreviations: BMI=body mass index; mg=milligrams; mmol/L= millimoles per litre, m²=square meter, n=number; N=total sample size; NR=not reported; ppFEV₁=percent predicted forced expiratory volume in 1 second; kg= kilogram, SD=standard deviation, wks=weeks
 Notes: a Definition 1 and Definition 2 differs across the trials, b Results are 144 weeks for patient enrolled in ENVISION and STRIVE that continued open-label extension study PERSIST
 Source: Table B (ii).6.1 p38 (KIWI, KLIMB), Table B (ii) 6.2 p40 (ENVISION/PERSIST, STRIVE/PERSIST) of the Commentary of Ivacaftor (November 2016), Table 2.5.3 p57, Table 2.5.4 p59, Table 2.5.5 p60, Table 2.5.6 p62, Table 2.5.7 p63, Table 2.5.9 p65, Table 2.5.10 p67, Table 2.5.11 p67 of the Submission

6.17 The PBAC previously considered it was plausible that the claim of superior efficacy and non-inferior safety of ivacaftor over BSC in patients aged 6 and older could be

reasonably extrapolated to patients aged 2-5 years (Ivacaftor, PSD November 2016, paragraph 6.23).

- 6.18 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 124 (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 and of ppFEV₁ outcomes (which were previously considered the primary endpoint upon which to assess the efficacy of ivacaftor) and the short duration (24 weeks) of Study 124.
- 6.19 The ESC considered that the submission’s claim of similar safety compared to patients aged 2 years and older may be reasonable noting that the safety profile of ivacaftor in Study 124 was comparable to that in patients aged 2-5 years in the KIWI trial (N=34, 33 patients with any AEs, 6 patients with SAEs, 11 patients with AEs leading to drug interruption and 1 patient with AEs leading to study drug withdrawal). However, the ESC noted that the long-term safety of ivacaftor was unknown.
- 6.20 The PSCR presented analyses of patients from the UK and US CF registries in 2014 (2 and 3 years following commercial availability in the UK and US, respectively) comparing ivacaftor treated patients with a matched cohort of untreated patients from Bessonova et al., 2018 (Figures 1 and 2 below).

Figure 1: Hospitalisations and pulmonary exacerbations in ivacaftor and matched comparator cohorts

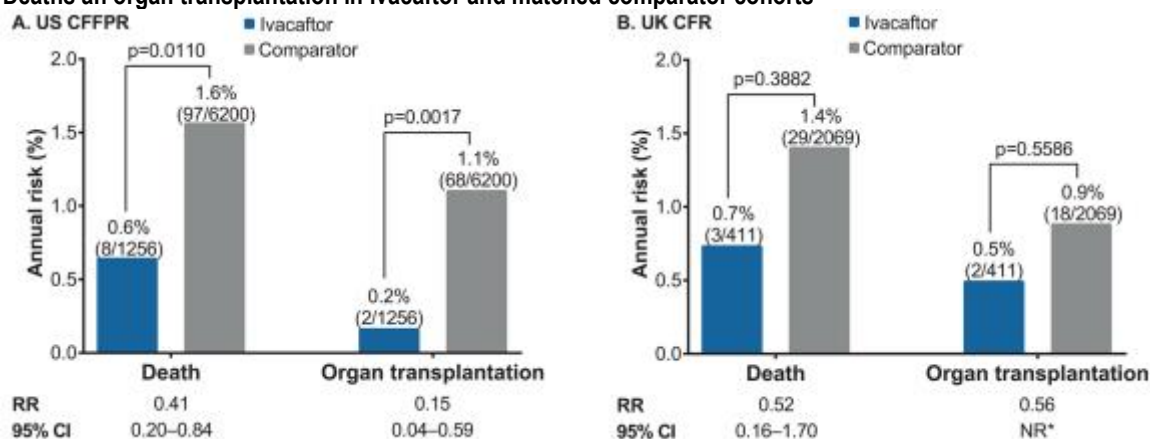


Source: Figure 1 of Bessonova et al., 2018

Notes: a Hospitalisation due to any reason, b PEx defined as the requirement of intravenous antibiotic use at home or in the hospital.

Abbreviations: CFFPR = Cystic Fibrosis Foundation Patient Registry; CFR = Cystic Fibrosis Registry; PEx = pulmonary exacerbations; RR = relative risk.

Figure 2: Deaths an organ transplantation in ivacaftor and matched comparator cohorts



Source: Figure 1 of Bessonova et al., 2018

Abbreviations: CFFPR = Cystic Fibrosis Foundation Patient Registry; CFR = Cystic Fibrosis Registry; PEx = pulmonary exacerbations; RR = relative risk.

- 6.21 The PSCR noted that ivacaftor-treated patients had fewer hospitalisations and pulmonary exacerbations as well as a statistically significant lower risk of death and organ transplantation. The PSCR noted that the risk of death and organ transplantation was not statistically significant between ivacaftor treated patients from the UK CF registry and matched controls however, considered this was likely due to the smaller sample size in the UK registry compared to the US registry. The PSCR indicated that these data provide evidence of long term efficacy of ivacaftor treatment. The ESC considered that while these data support a long-term treatment effect with ivacaftor, the applicability of these results to the Australian population is uncertain. The ESC noted that this data has not been evaluated as it was not provided with the submission.
- 6.22 Acknowledging the difficulties of obtaining clinical data in this population, the PBAC considered the claim of superior efficacy over BSC was reasonable in this context given the clinical efficacy demonstrated in previous studies in older age groups, and the evidence of biological activity as indicated by the sweat chloride response in Study 124. The PBAC considered that the claim of similar effectiveness compared with patients aged 2 years and older was uncertain although plausible.
- 6.23 The PBAC considered the claim of non-inferior safety to BSC was reasonable in this context noting there were no major safety signals in the context of the known safety profile of ivacaftor in older patients.

Economic analysis

- 6.24 The submission did not present an economic evaluation, on the basis of the small number of eligible patients in Australia (n=6) and an assumption that the cost-effectiveness would likely be similar to patients aged 2 years and older. This assumption is uncertain given that not all the efficacy outcomes presented were

directly comparable across the indications – most importantly, the lack of ppFEV₁ for 12 to 24-month olds.

- 6.25 The PBAC previously considered that as the incremental benefit of starting ivacaftor treatment at a younger age was unknown and difficult to demonstrate, the cost-effectiveness of the additional years of treatment was highly uncertain (Ivacaftor, PSD November 2016, paragraph 6.27). The same consideration would apply for the proposed listing: the cost-effectiveness of the additional year of treatment with ivacaftor, compared with BSC, is unknown; however, the ESC considered that the incremental cost per QALY gained of the additional year of treatment was likely to be high. The ESC noted that the intention of the previous submission for 2-5 year olds [REDACTED] The PBAC previously considered the intention of [REDACTED] was appropriate, given the difficulty in demonstrating the incremental benefit and therefore cost-effectiveness of earlier treatment with ivacaftor (ivacaftor, PSD November 2016, paragraph 7.7; see paragraph 3.2 and 3.3 for further details).
- 6.26 The Pre-PBAC Response provided results of an indicative cost-effectiveness analysis claiming this was performed using the same methodology used to estimate the cost-effectiveness for patients aged 2-5 years presented at the January 2017 meeting. The Pre-PBAC Response claimed that the cost per quality adjusted life year (QALY) for patients aged 12 – 24 months (of \$105,000/QALY - \$200,000/QALY) is similar to that for patients aged 2-5 years (of \$170,334/QALY) and patients aged 6+ years (of \$105,000/QALY - \$200,000/QALY). As this analysis was not presented with the submission, it has not been independently evaluated.
- 6.27 The requested price for 50 mg and 75 mg ivacaftor granules for patients aged 12-24 months is the same (AEMP \$22,500 per pack), whilst the price for ivacaftor tablets 150 mg is lower on a per mg basis, compared with the current listing for the granule formulation. The existing Deed of Agreement includes [REDACTED]; a similar arrangement would need to be applied to the requested listing.

Drug cost/patient/year:

- 6.28 The cost per pack of ivacaftor (28 days treatment) is \$22,500. The submission assumed 9.6 packs per patient per year are dispensed (after adjusting for use of CYP3A4 inhibitors and hepatic impairment), resulting in a total cost of \$216,000 per patient per year. Treatment is ongoing for the lifetime of the patient.

Estimated PBS usage & financial implications

- 6.29 This submission was not considered by DUSC. The 2018 DUSC analysis reported that since the listing of ivacaftor in December 2014, a total of 268 patients have been supplied ivacaftor for CF, fewer than predicted. However, the number of prescriptions

per patient was higher than predicted. The DUSC concluded that this might have been due to higher adherence and/or less dose reduction for patients with hepatic impairment or concomitant CYP3A4 inhibitors. The overall expenditure was close to that predicted in the submission (prior to performance rebates) (Ivacaftor DUSC, 2018).

6.30 The submission adopted an epidemiological approach in estimating the patient numbers. The submission estimated that less than 10,000 patients aged 12 to <24 months will be treated each year with ivacaftor granules. The number of patients may be underestimated as patients 12 to <24 months old who started treatment in Year 1 and who have not moved onto tablets in the subsequent years will be joined by newly diagnosed patients. In November 2016, in its consideration of the submission for patients aged 2-5 years, the PBAC noted that only if the number of newly diagnosed patients precisely matches the number of current patients moving onto ivacaftor tablets will the number of patients accessing ivacaftor granules remain static (Ivacaftor, PSD November 2016, paragraph 6.34). Moreover, while the submission stated that it included patients with other gating (class III) mutations, this could not be verified by the evaluation.

6.31 The overall financial impact for the Australian Government health budget over six years estimated by the submission is presented in Table 7.

Table 7: Overall impact on government health budgets

Description	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated number of patients to receive ivacaftor	█	█	█	█	█	█
Overall cost of ivacaftor to PBS (Not including performance-based rebate)	\$█	\$█	\$█	\$█	\$█	\$█
Overall net cost of ivacaftor to non-PBS services	\$█	\$█	\$█	\$█	\$█	\$█
Overall impact on government health budgets (not including performance-based rebate)	\$█	\$█	\$█	\$█	\$█	\$█

Source: Table 4.5.2, p88 of the submission

The redacted tablet shows that at Year 6, the estimated number of patients was less than 10,000 and the net cost to the PBS would be less than \$10 million.

Quality Use of Medicines

6.32 The submission did not present a discussion of quality use of medicine issues. However, the administration of ivacaftor granules mixed with food presents a wastage risk in very young children (potentially through regurgitation of the ivacaftor mixed with food, or refusal to eat, and drug stability of only one hour when mixed) (Ivacaftor,

PSD November 2016, paragraph 2.3). The ESC considered that wastage may have a considerable impact on cost-effectiveness of ivacaftor in clinical practice.

Financial Management – Risk Sharing Arrangements

6.33 The submission proposed increasing the number of patients in the patient number cap arrangement under the existing Risk Sharing Arrangement (RSA) to include patients aged 12 to <24 months. The submission proposed that if the patients aged 12 to <24 months are added to the PBS listing for ivacaftor, the patient number currently included in the RSA cap would need to be increased by the corresponding number (██████). The ESC noted that increasing the current caps to include these patients (12 to <24 months) assumes that ivacaftor is as cost-effective in this group as other indications which was not demonstrated by the submission, given it did not include an economic evaluation. The ESC noted that in its consideration of the November 2016 submission for ivacaftor for 2 to 5 year olds, the PBAC considered it would be possible to negotiate an arrangement to extend the listing for ivacaftor ██████████ (see paragraph 3.3). The ESC considered that in the absence of evidence demonstrating the incremental cost cost-effectiveness of ivacaftor in this setting, it would be appropriate to list ivacaftor at ██████████ such as by listing patients aged 12 to 24 ██████████. The PBAC has previously considered that the cost-effectiveness of commencing ivacaftor earlier is uncertain (see paragraph 6.25 above). However the PBAC noted the cost-effectiveness analysis provided by the sponsor subsequent to the November 2016 meeting suggested the cost per QALY was similar for the cohort aged 2-5 years and the cohort aged <6 years (see paragraph 3.4). The pre-PBAC Response stated that the sponsor was no longer requesting ██████████.

6.34 The ESC noted the existing pay-for-performance (PFP) scheme in place for ivacaftor requires patients' baseline ppFEV₁ values to be collected which would not be feasible for patients treated with ivacaftor granules from the age of 12 to 24 months. However the ESC noted that the current ivacaftor deed had reached the end of its term and that the conditions for the last year of the deed would be in effect until a new deed has been finalised. The PSCR indicated that the sponsor is currently in the process of finalising a new RSA with the ██████████.

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

7 PBAC Outcome

7.1 The PBAC recommended extending the Section 100 (Highly Specialised Drugs Program), Authority Required listing of ivacaftor granules to include treatment of CF

in patients aged 12 to <24 months who have a G551D mutation or other class III gating mutations in the CFTR gene.

- 7.2 The PBAC acknowledged that the consumer comments received from carers of patients with CF indicated strong support for earlier access to treatment.
- 7.3 The PBAC noted the submission was based on a 24-week single arm, open label study (Study 124) which assessed surrogate markers of treatment efficacy without ppFEV₁ outcomes. The PBAC noted that the magnitude of mean absolute improvement in sweat chloride (-73.5 mmol/L from baseline) was comparable to that previously observed in patients aged 2-5 years and ≥ 6 years. The PBAC also noted improvements in other outcome measures at 24 weeks for weight, length, FE-1 concentration and IRT concentration; however, the PBAC considered it was difficult to interpret these outcomes given the short duration of the trial.
- 7.4 The PBAC recalled that the primary outcome in clinical trials for ivacaftor for patients aged ≥ 2 years was absolute change in ppFEV₁ since baseline; however, the PBAC acknowledged the difficulties associated with assessing ppFEV₁ and obtaining clinical data in general, for this patient population. Based on the overall evidence, including the demonstrated clinical efficacy in older age groups, the PBAC considered the claim of superior efficacy over BSC was uncertain although plausible.
- 7.5 The PBAC recalled that the post hoc analysis presented at the January 2017 meeting of the treatment difference (ivacaftor versus placebo) for change from baseline in ppFEV₁ from the ENVISION trial for patients indicated similar ppFEV₁ responses in the 6-8 year age group compared with the older age groups, supported that the efficacy of ivacaftor is independent of age.
- 7.6 The PBAC noted there were no major safety signals associated with ivacaftor in this patient population in the context of the known safety profile of ivacaftor in older patients. The PBAC therefore considered that the claim of non-inferior safety was reasonable in this situation.
- 7.7 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]
- 7.8 The PBAC also recommended that the extension to the listing to include patients aged 12-24 months be flowed-on to the ivacaftor tablet form.
- 7.9 The PBAC did not consider that ivacaftor granules should be treated as interchangeable with any other drugs.

- 7.10 The PBAC advised that ivacaftor granules are not suitable for prescribing by nurse practitioners.
- 7.11 The PBAC recommended that the Early Supply Rule should apply.
- 7.12 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 Amend existing listings as follows:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
IVACAFTOR			
Ivacaftor 50 mg granules, 4 x 14 sachets	1	5	Kalydeco® Vertex Pharmaceuticals
Ivacaftor 75 mg granules, 4 x 14 sachets	1	5	(Australia) Pty Ltd

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Cystic Fibrosis
Treatment phase:	Initial treatment – New patients
Restriction:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	Patient must be assessed through a cystic fibrosis clinic/centre which is under the control of specialist respiratory physicians with experience and expertise in the management of cystic fibrosis. If attendance at such a unit is not possible because of geographical isolation, management (including prescribing) may be in consultation with such a unit; AND Patient must have G551D mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene on at least 1 allele; or Patient must have other gating (class III) mutation in the CFTR gene on at least 1 allele; AND Patient must have a sweat chloride value of at least 60 mmol/L by quantitative pilocarpine iontophoresis; AND Patient must not receive more than 24 weeks of treatment under this restriction; AND The treatment must be given concomitantly with standard therapy for this condition.
Population criteria:	Patient must be aged 12 months <u>2 years</u> or older.
Prescriber Instructions:	Patients receiving PBS-subsidised ivacaftor must be registered in the Australian Cystic Fibrosis Database Registry.

	<p>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.</p> <p>Dosage of ivacaftor must not exceed the dose of one tablet (150 mg) or one sachet twice a week, if the patient is concomitantly receiving one of the following strong CYP3A4 drugs inhibitors: boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole. Where a patient is concomitantly receiving a strong CYP3A4 inhibitor, a single supply of 56 tablets or sachets of ivacaftor will last for 28 weeks.</p> <p>Dosage of ivacaftor must not exceed the dose of one tablet (150 mg) or one sachet once daily, if the patient is concomitantly receiving one of the following moderate CYP3A4 inhibitors: amprenavir, aprepitant, atazanavir, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil. Where a patient is concomitantly receiving a moderate CYP3A4 inhibitor, a single supply of 56 tablets or sachets of ivacaftor will last for 8 weeks.</p> <p>Ivacaftor is not PBS-subsidised for this condition as a sole therapy.</p> <p>Ivacaftor is not PBS-subsidised for this condition in a patient who is currently receiving one of the following CYP3A4 inducers:</p> <p>Strong CYP3A4 inducers: avasimibe, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's wort</p> <p>Moderate CYP3A4 inducers: bosentan, efavirenz, etravirine, modafinil, nafcilin</p> <p>Weak CYP3A4 inducers: armodafinil, echinacea, pioglitazone, rufinamide.</p> <p>The authority application must be in writing and must include:</p> <ol style="list-style-type: none">(1) a completed authority prescription form; and(2) a completed Cystic Fibrosis 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 G551D mutation or other gating (class III) mutation on the CFTR gene; and(5) the result of a FEV1 measurement performed within a month prior to the date of application, if aged from 6 years or older. 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) a copy of a current medication history, including any CYP3A4 inhibitors and/or CYP3A4 inducers; and(7) a copy of a sweat chloride result; and(8) height and weight measurements at the time of application; and
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	(9) a baseline measurement of the number of days of CF-related hospitalisation (including hospital-in-the home) in the previous 12 months.
Administrative Advice:	<p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services</p> <p>Complex Drugs</p> <p>Reply Paid 9826</p> <p>HOBART TAS 7001</p> <p>Special Pricing Arrangements apply.</p> <p>No increase in the maximum number of repeats may be authorised.</p>

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Cystic Fibrosis
Treatment phase:	Continuing treatment
Restriction:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	<p>Patient must be assessed through a cystic fibrosis clinic/centre which is under the control of specialist respiratory physicians with experience and expertise in the management of cystic fibrosis. If attendance at such a unit is not possible because of geographical isolation, management (including prescribing) may be in consultation with such a unit;</p> <p>AND</p> <p>Patient must have received PBS-subsidised initial therapy with ivacaftor, given concomitantly with standard therapy, for this condition;</p> <p>AND</p> <p>Patient must not receive more than 24 weeks of treatment under this restriction;</p> <p>AND</p> <p>The treatment must be given concomitantly with standard therapy for this condition.</p>
Population criteria:	Patient must be aged <i>12 months</i> 2 years or older.
Prescriber Instructions:	Patients receiving PBS-subsidised ivacaftor must be registered in the Australian Cystic Fibrosis Database Registry.

	<p>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.</p> <p>Patients who have an acute infective exacerbation at the time of assessment for continuing therapy may receive an additional one month's supply in order to enable the assessment to be repeated following resolution of the exacerbation.</p> <p>Dosage of ivacaftor must not exceed the dose of one tablet (150 mg) or one sachet twice a week, if the patient is concomitantly receiving one of the following strong CYP3A4 drugs inhibitors: boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole. Where a patient is concomitantly receiving a strong CYP3A4 inhibitor, a single supply of 56 tablets or sachets of ivacaftor will last for 28 weeks.</p> <p>Dosage of ivacaftor must not exceed the dose of one tablet (150 mg) or one sachet once daily, if the patient is concomitantly receiving one of the following moderate CYP3A4 inhibitors: amprenavir, aprepitant, atazanavir, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil. Where a patient is concomitantly receiving a moderate CYP3A4 inhibitor, a single supply of 56 tablets or sachets of ivacaftor will last for 8 weeks.</p> <p>Ivacaftor is not PBS-subsidised for this condition as a sole therapy.</p> <p>Ivacaftor is not PBS-subsidised for this condition in a patient who is currently receiving one of the following CYP3A4 inducers:</p> <p>Strong CYP3A4 inducers: avasimibe, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's wort</p> <p>Moderate CYP3A4 inducers: bosentan, efavirenz, etravirine, modafinil, nafcillin</p> <p>Weak CYP3A4 inducers: armodafinil, echinacea, pioglitazone, rufinamide.</p> <p>The authority application must be in writing and must include:</p> <ol style="list-style-type: none">(1) a completed authority prescription form; and(2) a completed Cystic Fibrosis Ivacaftor Authority Continuing Application Supporting Information Form; and(3) the result of a FEV1 measurement performed within one month prior to the date of application, if aged 6 years or older. Note: FEV1, must be measured in an accredited pulmonary function laboratory, with documented no acute infective exacerbation at the time FEV1 is measured; and(4) a copy of a current medication history, including any CYP3A4 inhibitors and/or CYP3A4 inducers; and(5) height and weight measurements at the time of application; and(6) a measurement of number of days of CF-related hospitalisation (including hospital in the home) in the previous 6 months.
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Administrative Advice:	<p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services</p> <p>Complex Drugs</p> <p>Reply Paid 9826</p> <p>HOBART TAS 7001</p> <p>Special Pricing Arrangements apply.</p> <p>No increase in the maximum number of repeats may be authorised.</p>
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Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
IVACAFTOR				
Ivacaftor 150 mg tablet, 56	1	5	Kalydeco	Vertex Pharmaceuticals
	1	5	®	(Australia) Pty Ltd

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
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Clinical criteria:	<p>Patient must be assessed through a cystic fibrosis clinic/centre which is under the control of specialist respiratory physicians with experience and expertise in the management of cystic fibrosis. If attendance at such a unit is not possible because of geographical isolation, management (including prescribing) may be in consultation with such a unit;</p> <p>AND</p> <p>Patient must have G551D mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene on at least 1 allele; or</p> <p>Patient must have other gating (class III) mutation in the CFTR gene on at least 1 allele;</p> <p>AND</p> <p>Patient must have a sweat chloride value of at least 60 mmol/L by quantitative pilocarpine iontophoresis;</p> <p>AND</p> <p>Patient must not receive more than 24 weeks of treatment under this restriction;</p> <p>AND</p> <p>The treatment must be given concomitantly with standard therapy for this condition.</p>

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Population criteria:	Patient must be aged 12 months 2 years or older.
Prescriber Instructions:	<p>Patients receiving PBS-subsidised ivacaftor must be registered in the Australian Cystic Fibrosis Database Registry.</p> <p>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.</p> <p>Dosage of ivacaftor must not exceed the dose of one tablet (150 mg) or one sachet twice a week, if the patient is concomitantly receiving one of the following strong CYP3A4 drugs inhibitors: boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole. Where a patient is concomitantly receiving a strong CYP3A4 inhibitor, a single supply of 56 tablets or sachets of ivacaftor will last for 28 weeks.</p> <p>Dosage of ivacaftor must not exceed the dose of one tablet (150 mg) or one sachet once daily, if the patient is concomitantly receiving one of the following moderate CYP3A4 inhibitors: amprenavir, aprepitant, atazanavir, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil. Where a patient is concomitantly receiving a moderate CYP3A4 inhibitor, a single supply of 56 tablets or sachets of ivacaftor will last for 8 weeks.</p> <p>Ivacaftor is not PBS-subsidised for this condition as a sole therapy.</p> <p>Ivacaftor is not PBS-subsidised for this condition in a patient who is currently receiving one of the following CYP3A4 inducers:</p> <p>Strong CYP3A4 inducers: avasimibe, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's wort</p> <p>Moderate CYP3A4 inducers: bosentan, efavirenz, etravirine, modafinil, nafcilin</p> <p>Weak CYP3A4 inducers: armodafinil, echinacea, pioglitazone, rufinamide.</p> <p>The authority application must be in writing and must include:</p> <ol style="list-style-type: none"> (1) a completed authority prescription form; and (2) a completed Cystic Fibrosis 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 G551D mutation or other gating (class III) mutation on the CFTR gene; and (5) the result of a FEV1 measurement performed within a month prior to the date of application, if aged from 6 years or older. 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) a copy of a current medication history, including any CYP3A4 inhibitors and/or CYP3A4 inducers; and

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	<p>(7) a copy of a sweat chloride result; and</p> <p>(8) height and weight measurements at the time of application; and</p> <p>(9) a baseline measurement of the number of days of CF-related hospitalisation (including hospital-in-the home) in the previous 12 months.</p>
Administrative Advice:	<p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services</p> <p>Complex Drugs</p> <p>Reply Paid 9826</p> <p>HOBART TAS 7001</p> <p>Special Pricing Arrangements apply.</p> <p>No increase in the maximum number of repeats may be authorised.</p>

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Cystic Fibrosis
Treatment phase:	Continuing treatment
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Clinical criteria:	<p>Patient must be assessed through a cystic fibrosis clinic/centre which is under the control of specialist respiratory physicians with experience and expertise in the management of cystic fibrosis. If attendance at such a unit is not possible because of geographical isolation, management (including prescribing) may be in consultation with such a unit;</p> <p>AND</p> <p>Patient must have received PBS-subsidised initial therapy with ivacaftor, given concomitantly with standard therapy, for this condition;</p> <p>AND</p> <p>Patient must not receive more than 24 weeks of treatment under this restriction;</p> <p>AND</p> <p>The treatment must be given concomitantly with standard therapy for this condition.</p>
Population criteria:	Patient must be aged <i>12 months</i> 2 years or older.

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	(6) a measurement of number of days of CF-related hospitalisation (including hospital in the home) in the previous 6 months.
Administrative Advice:	<p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services</p> <p>Complex Drugs</p> <p>Reply Paid 9826</p> <p>HOBART TAS 7001</p> <p>Special Pricing Arrangements apply.</p> <p>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.