5.10 IVACAFTOR, Sachet containing granules 13.4 mg, Kalydeco®, Vertex Pharmaceuticals Pty Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested Section 100, Highly Specialised Drugs Program listing of a new strength of ivacaftor (IVA) (sachets containing 13.4 mg granules) for the treatment of cystic fibrosis (CF) in patients aged 1 to 4 months with either a G551D mutation or other gating (Class III) mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene on at least 1 allele, or at least one mutation in the CFTR gene that is responsive to IVA potentiation based on clinical and/or in vitro assay data.

1.2 Listing was requested on the basis of equity and clinical need; no economic evaluation was presented in the submission to support the listing requested in the proposed population.

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

Component	Description
Population	CF patients aged 1 to less than 4 months with either - G551D mutation or other gating (Class III) mutation in the CFTR gene on at least 1 allele, or - at least one mutation in the CFTR gene that is responsive to IVA potentiation based on clinical and/or in vitro assay data
Intervention	Ivacaftor granules, weight-based dosing
Comparator	BSC
Outcomes	Absolute change from baseline in sweat chloride 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 faecal elastase-1 Absolute change from baseline in immunoreactive trypsinogen Measures of pulmonary exacerbations
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

Source: unnumbered Table of the submission.
BSC = best supportive care; CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; IVA = ivacaftor

2 Background

Registration status

2.1 **TGA status at time of PBAC consideration***:* registered. The submission was made under the TGA/PBAC Parallel Process. At the time of evaluation for PBAC consideration, the TGA Clinical Evaluation report and Delegate's Overview were available.

2.2 Ivacaftor was included on the ARTG on the 6 February 2025 for the treatment of cystic fibrosis (CF) in patients aged 1 month and older who have at least one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay.

Previous PBAC consideration

2.3 The PBAC has considered ivacaftor on several occasions since July 2013 with the most recent consideration in November 2023, for use in patients aged 4 months and older who have at least one mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/or in vitro data. In reviewing that submission, the PBAC acknowledged the challenges associated with conducting clinical trials in younger patients and those with rare mutations. The PBAC considered that, overall, treatment with ivacaftor was likely to provide a clinical benefit in the requested populations; however, the magnitude of the benefit was uncertain (para 7.5, ivacaftor Public Summary Document (PSD), PBAC meeting November 2023).

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
Ivacaftor					
Ivacaftor, 13.4 mg granules, sachets	$21,375.00 published price $[redacted] / $[redacted][a] effective price	1	56	*2* ~~5~~	Kalydeco

[a] Public hospital DPMQ, Indication specific pricing.

Category / Program: ☒ Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)
Prescriber type: ☒ Medical Practitioners
Restriction Type – ☒Authority Required – non-immediate/delayed assessment by Services Australia
Authority type: ☒ Complex Authority Required (CAR)
Indication: *Cystic fibrosis*
Treatment Phase: Initial treatment- *New Patient (gating mutations)* /~~Continuing treatment (*gating mutations)*~~
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
Clinical criteria:
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**~~
~~**Clinical criteria:**~~

~~Patient must not receive more than 24 weeks of treatment under this restriction per authority application.~~
AND
Clinical criteria:
The treatment must be given concomitantly with standard therapy for this condition.
AND
Population criteria:
Patient must be aged 1 month or older
Prescribing Instructions: For the purposes of this restriction, the list of mutations considered to be responsive to ivacaftor is defined in the TGA approved Product Information
Prescribing Instructions: 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. 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.
Prescribing Instructions: Ivacaftor is not PBS-subsidised for this condition as a sole therapy. Ivacaftor is not PBS-subsidised for this condition in a patient who is currently receiving one of the following CYP3A4 inducers: Strong CYP3A4 inducers: avasimibe, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's wort Moderate CYP3A4 inducers: bosentan, efavirenz, etravirine, modafinil, nafcillin Weak CYP3A4 inducers: armodafinil, echinacea, pioglitazone, rufinamide.
Prescribing Instructions: The authority application must be in writing and must include: (1) a completed authority prescription; and (2) a completed Cystic Fibrosis Authority Application Supporting Information Form; and (3) details of the pathology report substantiating G551D mutation or other gating (Class III) mutation on the CFTR gene - quote each of the: *(i) the specific CFTR mutation listed in the TGA approved Product Information,* (ii) name of the pathology report provider, (iii) date of pathology report, (iv) unique identifying number/code that links the pathology result to the individual patient; and (4) current CYP3A4 inhibitors, CYP3A4 inducers and IV antibiotics; and ~~(5) sweat chloride result.~~
Administrative Advice: *Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).* *Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au* *Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos* *Or mailed to:* *Services Australia* *Complex Drugs* *Reply Paid 9826* *HOBART TAS 7001*
Administrative Advice: *No increase in the maximum number of repeats may be authorised.*

Administrative Advice: *Special Pricing Arrangements apply.*
Administrative Advice: *For the purposes of this restriction, the list of gating mutations are: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R.*

Category / Program: Section 100 – Highly Specialised Drugs Program
Prescriber type: ☒Medical Practitioners
Restriction Type – ☒Authority Required – non-immediate/delayed assessment by Services Australia
Authority type: ☒ Complex Authority Required (CAR)
Indication: *Cystic fibrosis*
Treatment Phase: Initial treatment ~~/Continuing treatment~~ - *New patient (non-gating mutations)*
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
Clinical criteria:
Patient must have at least one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data
AND
Clinical criteria:
Patient must not have either: (i) G551D mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene; (ii) other gating (class III) mutation in the CFTR gene
~~**AND**~~
~~**Clinical criteria:**~~
~~Patient must not receive more than 24 weeks of treatment under this restriction per authority application.~~
AND
Clinical criteria:
The treatment must be given concomitantly with standard therapy for this condition.
Population criteria:
Patient must be aged 1 month or older
Prescribing Instructions: For the purposes of this restriction, the list of mutations considered to be responsive to ivacaftor is defined in the TGA approved Product Information
Prescribing Instructions: 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. 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.
Prescribing Instructions: Ivacaftor is not PBS-subsidised for this condition as a sole therapy.

Ivacaftor is not PBS-subsidised for this condition in a patient who is currently receiving one of the following CYP3A4 inducers: Strong CYP3A4 inducers: avasimibe, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's wort Moderate CYP3A4 inducers: bosentan, efavirenz, etravirine, modafinil, nafcillin Weak CYP3A4 inducers: armodafinil, echinacea, pioglitazone, rufinamide.
Prescribing Instructions: The authority application must be in writing and must include: (1) a completed authority prescription; and (2) a completed Cystic Fibrosis Authority Application Supporting Information Form; and (3) details of the pathology report substantiating ~~G551D mutation or other gating (Class III) mutation on the CFTR gene -~~ *the specific mutation considered to be responsive to ivacaftor as listed in the TGA approved Product Information*. ~~q~~Quote each of the: *(i) the specific ~~CFTR~~ mutation listed in the TGA approved Product Information,* (ii) name of the pathology report provider, (iii) date of pathology report, (iv) unique identifying number/code that links the pathology result to the individual patient; and (4) current CYP3A4 inhibitors, CYP3A4 inducers and IV antibiotics; and ~~(5) sweat chloride result.~~
Administrative Advice: *Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).* *Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au* *Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos* *Or mailed to:* *Services Australia* *Complex Drugs* *Reply Paid 9826* *HOBART TAS 7001*
Administrative Advice: *No increase in the maximum number of repeats may be authorised.*
Administrative Advice: *Special Pricing Arrangements apply.*

3.2 The submission proposed that the current Special Pricing Arrangement, with indication specific effective pricing applying to the proposed new listing. The proposed ex-manufacturer price (EMP) for patients with gating mutations is $[redacted] per pack and for patients with non-gating mutations is $[redacted] per pack.

3.3 The pre-PBAC response agreed with the Secretariat's suggestions that (i) an initial restriction with 2 repeats of 56 packs would be sufficient to cater for the short duration of use between 1-4 months of age and (i) sweat chloride results be removed from the restriction to align with other recently listed CFTR modulators.

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

4 Population and disease

4.1 CF is a rare genetic disease that is caused by mutations in the CFTR gene which impair ion transport across epithelial membranes, causing thick mucus to accumulate within the lungs and obstructing the function of the liver, pancreas, and other organs, resulting in significant morbidity, reduced quality of life and premature mortality.

4.2 CFTR modulators (CFTRm) have been used to treat CF for the last 10 years or more. Initially, clinical trial evidence was used to establish the efficacy of ivacaftor for disease caused by the G551D mutation, but over time, the number of mutations thought to be responsive to treatment has expanded and now includes rare mutations.

5 Comparator

5.1 The submission nominated best supportive care as the comparator. As part of its consideration in November 2023 (see paragraph 2.3), the PBAC considered that the nomination of best supportive care as the comparator was reasonable; however, it would have been informative to compare commencing treatment with ivacaftor at 4 months of age with commencing treatment with other CFTRm at an older age for some populations (para 7.4, ivacaftor PSD, PBAC meeting November 2023).

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

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 (4) and organisations (2) via the Consumer Comments facility on the PBS website. The comments from individuals described the benefits of treatment with ivacaftor as life-changing stating early access will extend the lives of children afflicted with CF, prevent irreversible scarring of the lungs and lead to better health outcomes. The comments noted the positive improvement in health and quality of life.

6.3 Cystic Fibrosis Australia strongly supported expanding access for infants with CF aged 1 to less than 4 months as early intervention can significantly improve health outcomes and quality of life. It was noted that initiating ivacaftor therapy in infants can maintain healthier lung function, improve weight gain, and reduce complications. CF Together also provided strong support for ivacaftor being available for CF patients aged 1 to less than 4 months of age.

Clinical studies

6.4 The submission was based on two studies: Study VX-15-770-124-Cohort 8 in patients aged 1 to < 4 months and Study VX15-770-126 in patients aged < 24 months.

6.5 Details of the studies presented in the submission are provided in Table 2.

Table 2: Trials (and associated reports) presented in the submission

Trial ID	Protocol title/publication title	Publication citation
Study 124 VX15-770-124 NCT02725567	A Phase 3, 2-Part, Open-label 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 an Ivacaftor-Responsive *CFTR* Mutation. Analysis of Subjects 1 to <4 Months of Age (Part A/B Cohort 8)	Clinical Study Report, Interim Analysis 4, September 2022
	McNally P, Singh A, McColley SA, Davies JC, Higgins M, Liu M, Lu J, Rodriguez-Romero V, Shih JL, Rosenfeld M; VX15-770-124 Study Group. Safety and efficacy of ivacaftor in infants aged 1 to less than 4 months with cystic fibrosis.	*J Cyst Fibros*. 2024 May;23(3):429-435. doi: 10.1016/j.jcf.2024.03.012.
Study 126 VX15-770-126 NCT03277196	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	Clinical Study Report 1.0, 14 February 2024

Source: Table 2.1, p31 of the submission.

6.6 The key features of the studies are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
VX15-770-124 Cohort 8	7	OL, MC, single arm, 24 wk	High	CF, sweat chloride ≥ 60 mmol//L, age 1 to <4 mo; born at ≥ 38 wk; weight ≥3kg aged 1 to <3 mo and ≥5 kg aged 3 to <4 mo; most patients had G551D or F508del (or both).	Safety and pharmacokinetics (co-primary); pharmacodynamics (secondary); efficacy (tertiary).
VX15-770-126	86	OL, MC, single arm, 96 wk; observation cohort planned but no patients were enrolled.	High	Age < 24 mo; patients completing 24 wk treatment in VX15-770-124 (N = 38) *or* enrolled in VX15-770-124 Part A only *or* not previously exposed to IVA (N = 48); 46/86 had G551D + F508del and 83/86 had either G551D or F508del.	Safety (primary); pharmacokinetics (secondary); efficacy (tertiary).

Source: VX15-770-124 CSR; VX15-770-126 CSR
CF = cystic fibrosis; IVA. = ivacaftor; MC = multi-centre; mo = months; OL = open label.

6.7 Of the seven subjects in Cohort 8 of VX15-770-124, two patients had *G115D/F508del* genotype and two had at least one copy of *G115D*. Of the 86 patients in VX-15-770-126, 68 (79.1%) had at least one copy of *G551D*. The evaluation noted neither of these studies provided any meaningful data on patients with mutations other than *G551D*.

Comparative effectiveness

6.8 It is impractical to measure lung function in very small children. Sweat chloride was presented as evidence of ivacaftor effect. The submission presented the same discussion of the significance of change in sweat chloride as for the submission for ivacaftor in November 2023 (para 6.67, ivacaftor PSD, November 2023 PBAC meeting).

6.9 Other outcomes previously considered by PBAC as relevant are nutritional status, pulmonary exacerbations and fecal elastase-1 as an indication of pancreatic insufficiency.

6.10 Efficacy data are shown in Table 4.

Table 4: Efficacy outcomes in the submitted studies.

	VX15-770-124 N = 7		**VX15-770-126 N = 86**	
	Baseline	**Absolute Change from Baseline to 24 wk[1]**	**Baseline**	**Absolute Change from Baseline to 96 wk**
Sweat Chloride, mmol/L				
n	7	5	86	33
Mean (SD)	73.8 (19.1)	-32.9 (33.8)	95.1 (17.9)	-55.3 (25.0)
Median (range)	69.0 (49.0, 103.0)	-56.0(-60.0, -8.5)	100.0 (39.5, 120.5)	-60.5 (-93.0, 0.0)
Weight for Age, z-score				
n	7	6	86	51
Mean (SD)	-0.88 (1.0)	1.14 (0.89)	0.02 (0.96)	0.44 (0.84)
Median (range)	-1.32 (-1.93, 0.70)	1.01 (0.14, 2.66)	-0.03 (-2.88, 2.07)	0.44 (-0.89, 2.20)
Fecal elastase-1, mcg/g				
n	6	5	82	33
Mean (SD)	344.8 (197.5)	417.2 (185.1)	213.4 (214.8)	225.6 (202.4)
Median (range)	424.5 (31.0, 500.0)	500.0 (86.0, 500.0)	103.5 (7.5, 500.0)	272.0 (-94.0, 492.5)

Source: VX15-770-124 CSR, Table 11-2, p46; Table 11-3, p48; Table 11-4, pp52-53; VX15-770-124 CSR, Table 11-1, pp38-39; Table 11-2, pp41-42.

mcg = microgram; SD = standard deviation.

[1] Except for sweat chloride, for which data are at 12 weeks: only one subject had sweat chloride data for week 24 and this subject showed no change in sweat chloride at this assessment.

6.11 In VX15-770-126 nutritional parameters were normal at baseline and although they tended to increase during treatment the significance of this is unclear, especially in the context of missing data.

6.12 Higher levels of fecal elastase-1 are associated with improved pancreatic function, and the PBAC has previously accepted levels lower than 200mcg/g as indicative of pancreatic insufficiency (paragraph 6.14, ivacaftor PSD, PBAC Meeting November 2023). Fecal elastase-1 was above 200 mcg/g at baseline in most patients in VX15-770-124, and although the mean and median values increased at 24 weeks treatment, it was not reported whether the level in any patient crossed the threshold indicating pancreatic insufficiency. Similarly, in VX15-770-126, mean and median fecal elastase-1 were higher at 96 weeks but whether patients crossed the pancreatic insufficiency threshold was not reported.

6.13 In both studies, pulmonary exacerbations were defined by a combination of antibiotic treatment (oral, inhaled, or intravenous) and clinical criteria. Two sets of clinical criteria were used; List A: oxygen saturation < 90% breathing room air, or ≥5% fall from baseline; new lobar infiltrates or atelectasis on CXR; hemoptysis (more than

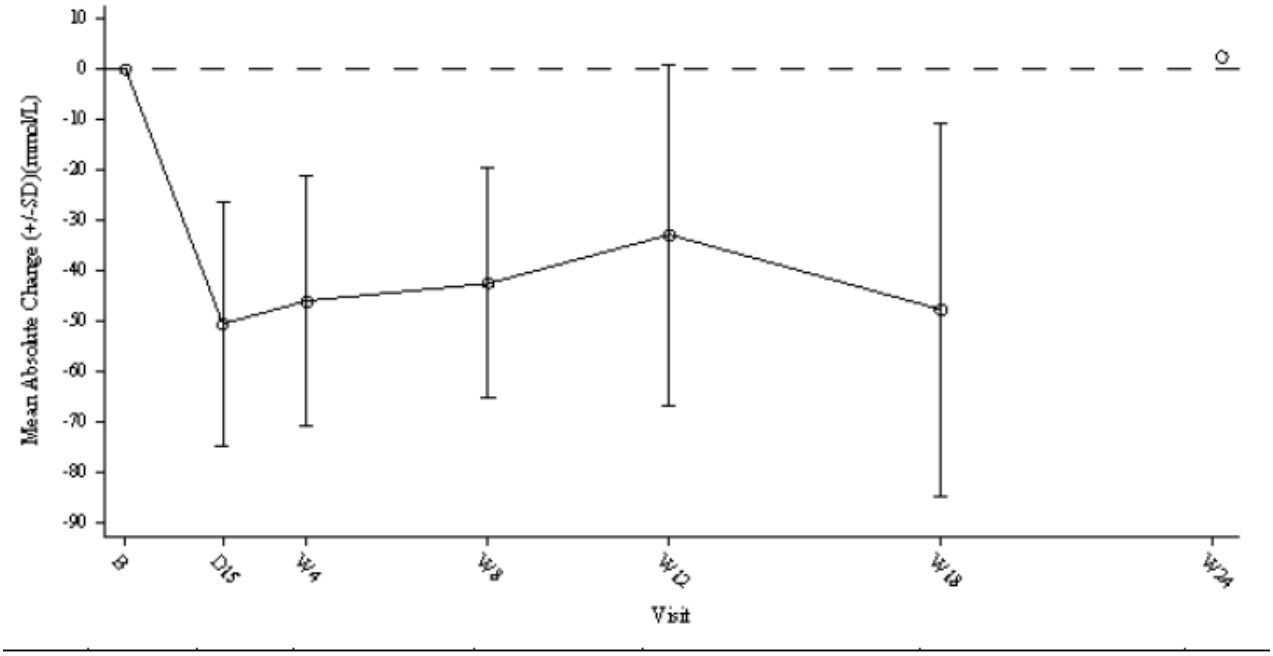
streaks more than once); List B: increased respiratory rate for ≥3 days; new or increased adventitial lung sounds; increased cough for ≥3 days; increased sputum for ≥3 days. Because there is no accepted clinical definition of pulmonary exacerbation in this age group, data were collected using two definitions: Definition 1 = antibiotic treatment plus any criterion from List A or List B; Definition 2 = antibiotic treatment plus one List A criterion or two List B criteria.

6.14 There were no recorded pulmonary exacerbations by either definition during treatment in VX15-770-124.

6.15 In VX15-770-126, by Definition 1, 40 (46.5%) patients had 117 exacerbations (events/year = 0.89). By Definition 2, 24 (27.9%) subjects had 51 exacerbations (events/year = 0.39). It is difficult to compare these results to those observed in trials in older patients because the definition of an exacerbation was not consistent across trials.

6.16 Change in sweat chloride by study visit in Cohort 8 of VX15-770-124 are shown in Figure 1.

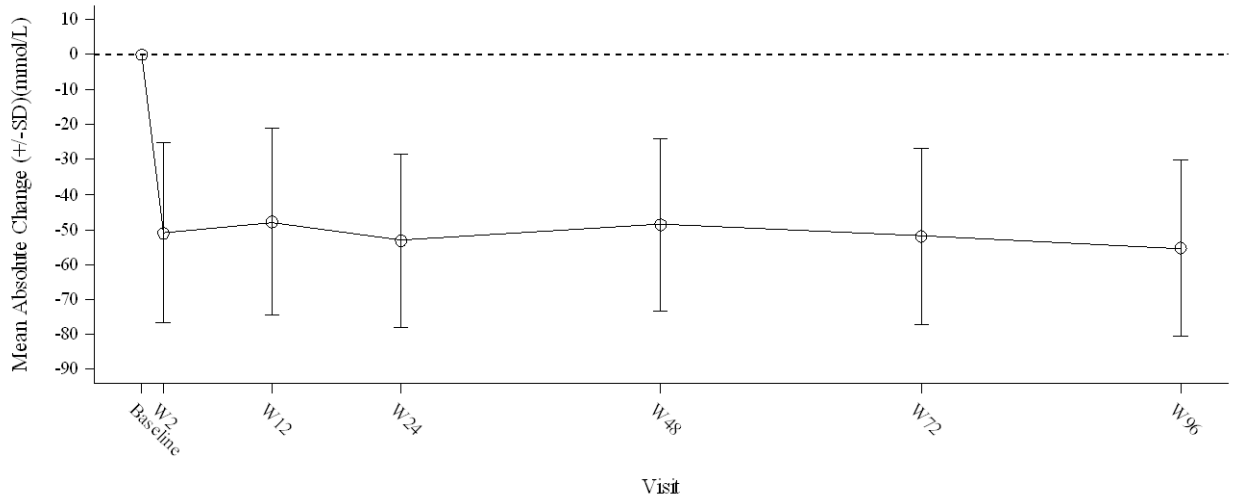
Figure 1: Change from baseline in sweat chloride in Cohort 8 in VX15-770-124



Source: Figure 2.2, p40 of the submission.
B = baseline; D = day; IVA, ivacaftor; n = number of patients contributing data; W, week.
One subject discontinued study drug treatment at Week 9, but did not discontinue the study until Week 24. Data for this subject were included in the efficacy analyses.

6.17 Changes in sweat chloride by study visit in VX15-770-126 are shown in Figure 2.

Figure 2: Change from baseline in sweat chloride to 96 weeks in VX15-770-126



Source: Figure 2.6, p52 of the submission. W = week.

Comparative harms

6.18 Adverse events in the studies are shown in Table 5.

Table 5: Adverse events in the submitted studies.

	VX15-770-124 N = 7	VX15-770-126 N = 86
Duration of Treatment, weeks Mean (SD) Median (range)	 22.0 (5.7) 24.0 (9, 25)	 80.0 (27.6) 96.1 (5.1, 99.1)
Treatment Duration Category, n (%) ≤24 wk[1] >24 but ≤72 wk >72 wk	 6 (85.7) - -	 6 (7.0%) 16 (18.6%) 64 (74.4%)
Patients with AEs, n (%)	4 (57.1%)	85 (99%)
Total AEs	14	968
Patients with SAEs n, (%)	0	21 (24.4%)
Total SAEs	0	36
Patients with AE leading to discontinuation of ivacaftor, n (%)	1 (14.3%)	2 (2.3%)
Patients with AE leading to interruption of ivacaftor, n (%)	-	8 (9.3%)
ALT elevated, n (%) ≤2 x ULN >2 but ≤3 x ULN >3 x ULN	5 (71.4%) 3 (42.9%) 1 (14.3%) 1 (14.3%)	30 (34.9%) 24 (27.9%) 1 (1.2%) 5 (5.8%)
AST elevated, n (%) ≤2 x ULN >2 but ≤3 x ULN >3 x ULN	 - - 1 (14.3%)	11 (12.8%) 9 (10.5%) 2 (2.3%) -
Total bilirubin elevated, n (%) >2 x ULN	1 (14.3%) 1 (14.3%)	0 0
Rash, n (%)	-	21 (24.4%)

Source: VX15-770-124 CSR, Table 12-2, p60; Table 12-2, pp60-61; Table 12-4, p64; VX15-770-126 CSR, Table 12-1, p56, Table 12-2, p57, Table 12-5, p61.
AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; SAE = serious adverse event; SD. = standard deviation.
[1] One patient discontinued treatment at week 9 because of abnormal liver function.

6.19 As in other studies of ivacaftor, rash and liver function abnormalities were common.

Benefits/harms

6.20 The data presented in the submission did not allow for a comparison of the benefits and harms of ivacaftor vs best supportive care in this population. Accordingly, a benefits/harms table has not been presented.

Clinical claim

6.21 The submission described ivacaftor as superior in terms of effectiveness and comparable in terms of safety to best supportive care in infants aged 1-4 months with either a *G551D* mutation or other gating (Class III) mutation in the *CFTR* gene on at least one allele, or at least one mutation in the *CFTR* gene that is responsive to IVA potentiation based on clinical and/or *in vitro* assay data.

6.22 With regard to effectiveness, the evaluation considered the claim was not adequately supported. The submitted data, taken as a whole, support a conclusion that ivacaftor increases the activity of the CFTR in infants aged 1-4 months with the *G551D* or other

gating (Class III) mutation. No evidence was submitted that this results in clinical benefit. The great majority of patients in the submitted data had the *G551D* genotype.

6.23 With regard to safety, the evaluation considered the claim was not adequately supported. In VX15-770-126 adverse events of rash and liver function test abnormalities were common, and required interruption of treatment. No data was submitted to show that these adverse events are less common in infants aged 1-4 months, or equally common in patients in this age group receiving BSC.

6.24 The PBAC considered that the claim of superior comparative effectiveness was uncertain.

6.25 The PBAC considered that the claim of comparable safety to best supportive care was unable to be supported by the data.

Economic analysis

6.26 The submission did not present an economic analysis. The submission stated that the request for reimbursement is based on equity and the expected benefit of treatment in these patients.

Drug/ cost/patient

Table 6: Drug cost per patient aged 1-4 months for ivacaftor, as applied in financial estimates

	Gating population	Non-gating population
Cost per 28 day pack (effective price)	$ [redacted]	$ [redacted]
Compliance	100%	100%
Cost per 3 months treatment (3.26 scripts)[a]	$ [redacted]	$ [redacted]

Source: constructed during the evaluation from the information in the submission. [a] 365.25/28/12*3

Estimated PBS usage & financial implications

6.27 This submission was not considered by DUSC.

6.28 The submission used an epidemiological approach to estimate the number of patients aged 1-4 months who would be diagnosed with CF, with either a G551D or other gating Class III mutation or at least one mutation responsive to IVA potentiation based on clinical and/or in vitro assay data. The estimates were based on data from the Australian Cystic Fibrosis Data Registry. The submission stated that the approach used was consistent with that used in the PBAC submission for IVA therapy for patients with CF aged 4-12 months of age. The key inputs for the financial estimates are shown in Table 7.

Table 7: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Prevalent population	The prevalence of CF patients aged < 12 months was based on the ACFDR data.	Yearly growth of 3.6% assumed
Uptake rate	[redacted]% per year	Based on the expected uptake in the November 2023 submission (for patients aged 4 to < 12 months)
Compliance rate	Assumed to be 100% for the 1-4 month age treatment period	
Effective prices for ivacaftor, per 28 day pack irrespective of formulation	Gating mutation: $[redacted] Non-gating mutation: $[redacted]	
Scripts per year	13.04; adjusted for this indication to 3.26	All patients under 12 months of age assumed to receive 3.26 scripts
MBS item	One additional liver function test, MBS item $17.70	Consistent with the November 2023 submission (for patients aged 4 to < 12 months)

Source: constructed from Tables 4.1 and 4.2, p62 and text in section 4 of the submission.
ACFDR = Australian Cystic Fibrosis Data Registry; CF = cystic fibrosis

6.29 The total number of patients treated, scripts dispensed and cost to the PBS, using the current effective prices of ivacaftor, are shown in Table 8. There was not expected to be any impact on use of other medicines.

Table 8: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated – gating mutation	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of patients treated- non-gating mutation	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed[a] – gating mutation	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed[a] – non- gating mutation	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Net financial implications						
Net cost to PBS/RPBS	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Net cost to MBS	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Net cost to PBS/RPBS/MBS	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]

Source: Tables 4.3,4.4, 4.6, 4.10, 4.13 of the submission.
[a] Assuming an additional 3.26 scripts (i.e., 4 months of treatment) per patient
The redacted values correspond to the following ranges:
[1] < 500
[2] $0 to < $10 million

6.30 The total cost to the PBS/RPBS of listing ivacaftor was estimated to be 0 to < $10 million in Year 6, and a total of 0 to < $10 million in the first 6 years of listing.

Financial Management – Risk Sharing Arrangements

6.31 The submission proposed that the requested population be included in the existing Deed of agreement for CFTR modulators, with no change to the subsidisation caps.

6.32 Information for the shared CF cap is provided in Table 9. Ivacaftor was included in the shared cap in June 2024.

Table 9: Current RSA for IVA, LUM/IVA, TEZ/IVA and ELX/TEZ/IVA ([redacted]% rebate for expenditure over the cap)

Cap Year	Cap Threshold ($)	Total Commonwealth payment ($)	% market share by drug	% of Cap reached
1 Year (Apr-22 – Mar 23)	[redacted]	[redacted]	LUM/IVA: [redacted]%; TEZ/IVA: [redacted]%; ELX/TEZ/IVA: [redacted]%	[redacted]%
2 Year (Apr-23 – Mar 24)	[redacted]	[redacted]	LUM/IVA: [redacted]%; TEZ/IVA: [redacted]% ELX/TEZ/IVA:[redacted]%	[redacted]%
3 Year (Apr-24 – Mar 25)	[redacted]	[redacted]	LUM/IVA: [redacted]%; TEZ/IVA: [redacted]% ELX/TEZ/IVA:[redacted]%; IVA 6%	[redacted]%
4 Year (Apr-25 – Mar 26)	[redacted]			
5 Year (Apr-26 – Mar 27)	[redacted]			

Source: Department of Health
ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; IVA = ivacaftor; LUM/IVA = lumacaftor/ivacaftor; TEZ/IVA = tezacaftor/ivacaftor
Note: Year 3 contains 10 months of data only and the draft amounts may change subject to end of financial year adjustments.

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

7 PBAC Outcome

7.1 The PBAC recommended the Section 100 (Highly Specialised Drugs Program) listing of ivacaftor granules 13.4 mg for the treatment of cystic fibrosis (CF) in patients aged 1 month to less than 4 months who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to ivacaftor based on clinical and/ or *in vitro* assay data. The PBAC noted that, overall, the evidence supporting the clinical claim in the submission was very limited but acknowledged the difficulties in obtaining clinical data in this population. The PBAC considered ivacaftor was likely to be cost-effective for this population at the current PBS price. The PBAC advised this population could be included in the current risk sharing arrangement for CFTR modulators with no increase in expenditure caps.

7.2 The PBAC acknowledged the consumer comments strongly supported the extension of the listing for ivacaftor.

7.3 The PBAC advised the amendments to the restriction criteria proposed by the Secretariat in Section 3 were reasonable.

7.4 The PBAC considered that the nomination of best supportive care (BSC) as the comparator was reasonable; however, as raised previously (see paragraph 5.1), it would have been informative to compare commencing treatment at 1 month of age with commencing treatment at 4 months of age.

7.5 The PBAC noted the submission presented data from one single arm study in patients aged 1 to 4 months of age (n=7) and one single arm study in patients aged less than 24 months of age (n=86) to support the clinical claim that ivacaftor is superior to BSC in terms of efficacy. The PBAC noted most patients had a *G551D* mutation and there was limited data on patients with non-gating mutations. The PBAC noted treatment with ivacaftor resulted in a reduction in sweat chloride over time (see Figure 1 and Figure 2). The PBAC noted other outcomes improved after treatment with ivacaftor (nutritional status, pulmonary exacerbations, fecal elastase-1) but limited conclusions could be drawn given the small patient numbers. The PBAC considered that, overall, treatment with ivacaftor was likely to provide a clinical benefit in patients aged 1 month to less than 4 months with gating or responsive mutations compared to best supportive care; however, the magnitude of benefit was uncertain.

7.6 The PBAC recalled it had previously accepted the claim that ivacaftor had comparable safety to BSC (paragraph 7.6, ivacaftor PSD, November 2023 PBAC meeting) and the adverse events observed in the younger population were similar to that observed in other populations.

7.7 The PBAC noted no economic evaluation was presented, with the sponsor requesting ivacaftor be made available for the additional patients at the same price as it is currently reimbursed through the PBS on the basis of equity and the expected benefit of treating patients at a younger age. The PBAC recalled it had initially recommended the listing of CFTR modulators with high and likely underestimated incremental cost effectiveness ratios on the basis of high clinical need. The PBAC noted that, over time, expanded populations (i.e., for younger patients and those with rarer mutations) have been recommended for listing. The PBAC noted the magnitude of clinical benefit is less certain in the expanded populations, and this may result in use that is less cost effective overall.

7.8 The PBAC recalled that in November 2023 it had considered it unlikely ivacaftor would be cost effective at the requested price (i.e., cost per pack of $[redacted] as per the gating population price outlined in Table 6), given its cost per patient per year was substantially higher than the current CFTR modulators and that most patients will transition to a CFTR modulator at an older age. The PBAC noted that with the March 2025 recommendation of ELX/TEZ/IVA for patients who have at least one mutation in the CFTR gene that is responsive to ELX/TEZ/IVA based on clinical and/or *in vitro* assay data, all patients aged 1 month to less than 4 months of age eligible for ivacaftor could transition to ELX/TEZ/IVA at 2 years of age.

7.9 The PBAC considered that the methodology for estimating the number of additional patients that would be eligible for ivacaftor and the estimated financial impact was reasonable.

7.10 The PBAC advised that the extended population should be included in the existing Risk Sharing Arrangement with no increase in expenditure caps as proposed in the submission (see paragraph 6.31).

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

a) Based on the available evidence the magnitude of benefit of treatment with ivacaftor was not able to be quantified, and therefore the criteria of having a substantial and clinically relevant improvement in efficacy compared to best supportive care was not met;

b) The treatment is not expected to address a high and urgent unmet clinical need as patients would have access to ivacaftor from 4 months of age;

c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

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

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
IVACAFTOR					
Ivacaftor 13.4 mg granules, 56 sachets	NEW HSD (Public) NEW HSD (Private)	1	56	2	Kalydeco
Restriction Summary [variant of: 15256] / Treatment of Concept: [variant of: 15251]					
Concept ID (for internal Dept. use)	Category / Program: ☒ Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)				
	Prescriber type: ☒ Medical Practitioners				
	Restriction Type – ☒Authority Required – non-immediate/delayed assessment by Services Australia				
	Authority type: ☒ Complex Authority Required (CAR)				
	Indication: *Cystic fibrosis*				
	Treatment Phase: Initial treatment- New Patient (gating mutations)				
	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				
	Clinical criteria:				
	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				
	Clinical criteria:				
	The treatment must be given concomitantly with standard therapy for this condition.				
	AND				
	Population criteria:				
	Patient must be aged 1 month or older				
	Prescribing Instructions: For the purposes of this restriction, the list of mutations considered to be responsive to ivacaftor is defined in the TGA approved Product Information				
	Prescribing Instructions: 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. 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.				
	Prescribing Instructions: Ivacaftor is not PBS-subsidised for this condition as a sole therapy.				

	Ivacaftor is not PBS-subsidised for this condition in a patient who is currently receiving one of the following CYP3A4 inducers: Strong CYP3A4 inducers: avasimibe, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's wort Moderate CYP3A4 inducers: bosentan, efavirenz, etravirine, modafinil, nafcillin Weak CYP3A4 inducers: armodafinil, echinacea, pioglitazone, rufinamide.
	Prescribing Instructions: The authority application must be made via the Online PBS Authorities System, or in writing via HPOS form upload or mail and must include: (1) details of the pathology report substantiating G551D mutation or other gating (Class III) mutation on the CFTR gene - quote each of the: (a) the specific CFTR mutation listed in the TGA approved Product Information, (b) name of the pathology report provider, (c) date of pathology report, (d) unique identifying number/code that links the pathology result to the individual patient; and (2) current CYP3A4 inhibitors, CYP3A4 inducers and IV antibiotics
	Prescribing Instructions: If the application is submitted through HPOS form upload or mail, it must include: (i) details of the proposed prescription; and (ii) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Administrative Advice: For the purposes of this restriction, the list of gating mutations are: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R.

Initial treatment (Non- Gating mutations)

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
IVACAFTOR					
Ivacaftor 13.4 mg granules, 56 sachets	NEW HSD (Public) NEW HSD (Private)	1	56	2	Kalydeco
Restriction Summary [variant of: 15254] / Treatment of Concept: [variant of: 15253]					
Concept ID (for internal Dept. use)	Category / Program: Section 100 – Highly Specialised Drugs Program				
	Prescriber type: ☒Medical Practitioners				
	Restriction Type – ☒Authority Required – non-immediate/delayed assessment by Services Australia				
	Authority type: ☒ Complex Authority Required (CAR)				

	Indication: Cystic fibrosis
	Treatment Phase: Initial treatment ~~/Continuing treatment~~ - *New patient (non-gating mutations)*
	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
	Clinical criteria:
	Patient must have at least one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data
	AND
	Clinical criteria:
	Patient must not have either: (i) G551D mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene; (ii) other gating (class III) mutation in the CFTR gene
	AND
	Clinical criteria:
	The treatment must be given concomitantly with standard therapy for this condition.
	Population criteria:
	Patient must be aged 1 month or older
	Prescribing Instructions: For the purposes of this restriction, the list of mutations considered to be responsive to ivacaftor is defined in the TGA approved Product Information
	Prescribing Instructions: 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. 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.
	Prescribing Instructions: Ivacaftor is not PBS-subsidised for this condition as a sole therapy. Ivacaftor is not PBS-subsidised for this condition in a patient who is currently receiving one of the following CYP3A4 inducers: Strong CYP3A4 inducers: avasimibe, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's wort Moderate CYP3A4 inducers: bosentan, efavirenz, etravirine, modafinil, nafcillin Weak CYP3A4 inducers: armodafinil, echinacea, pioglitazone, rufinamide.
	Prescribing Instructions: The authority application must be made via the Online PBS Authorities System, or in writing via HPOS form upload or mail and must include: (1) details of the pathology report substantiating the specific mutation considered to be responsive to ivacaftor as listed in the TGA approved Product Information. Quote each of the: (a) the specific mutation listed in the TGA approved Product Information, (b) name of the pathology report provider, (c) date of pathology report, (d) unique identifying number/code that links the pathology result to the individual patient; and (2) current CYP3A4 inhibitors, CYP3A4 inducers and IV antibiotics
	Prescribing Instructions:

	If the application is submitted through HPOS form upload or mail, it must include: (i) details of the proposed prescription; and (ii) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.

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

9 Context for Decision

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

10 Sponsor's Comment

Vertex welcomes the recommendation by the Pharmaceutical Benefits Advisory Committee (PBAC), to expand the PBS listing of KALYDECO® (ivacaftor) to include babies aged 1 to 4 months with at least one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data. This is an important first step to achieving reimbursed access for eligible patients in Australia.