5.08 IVACAFTOR, granules, 50 mg and 75 mg sachets, 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 a new presentation of ivacaftor, in the form of granules for treatment of cystic fibrosis (CF) in patients who have a G551D mutation or other class III gating mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene and to allow both the tablets and the granules to be used in patients with this condition aged 2 to 5 years.

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat are indicated in italics and strikethrough for deletions.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
IVACAFTOR				
Granule 50 mg	56	5	$[redacted]*	Kalydeco® Vertex Pharmaceuticals
Granule 75mg	56	5	$[redacted]*	
Tablet 150 mg	56	5	$[redacted]	

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Condition:	Cystic Fibrosis
PBS Indication:	Cystic Fibrosis
Treatment phase:	Initial – New patients
Restriction Level / Method:	☒ Authority Required - In Writing
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 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 2 years of age or older*, and over 8 kg of body weight.* Patients receiving PBS-subsidised ivacaftor must be registered in the Australian

	Cystic Fibrosis Database Registry. Treatment must not be given to a patient who has an acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease in the last 4 weeks prior to commencing this drug. Dosage of ivacaftor must not exceed the dose of one tablet 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.~~ *ketoconzale, itraconazole, posaconazole, viriconazole, telithromycin, and clarithromycin.* 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 50 mg daily with a body weight ≥*8 kg to* < 14 kg; 100 mg daily with a body weight ≥14 kg to <25 kg, and 150 mg daily with a body weight ≥25 kg, if the patient is concomitantly receiving one of the following moderate CYP3A4 inhibitors: ~~amprenavir, aprepitant, atazanavir, darunavir/ritonavir, diltiazem, ery*thromycin, fluconazole, fosamprenavir, imatinib, verapamil.*~~ *fluconazole and erythromycin.* 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. 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~~ —*rifampicin, rifabutin, phenobarbital, carbamazepine, phenytoin and St. John's wort (Hypericum perforatum).* ~~Moderate CYP3A4 inducers: bosentan, efavirenz, etravirine, modafinil, nafcillin~~ ~~Weak CYP3A4 inducers: armodafinil, echinacea, pioglitazone, rufinamide.~~ *Moderate to weak CYP3A4 inducers: dexamethasone, high-dose prednisone.* The authority application must be in writing and must include: (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) for patients 6 years of age or older, the result of a FEV1 measurement performed within a month prior to the date of application. Note: FEV1, must be measured in an accredited pulmonary function laboratory, with documented no acute infective exacerbation at the time FEV1 is measured; and (6) evidence that the patient has either chronic sinopulmonary disease or gastrointestinal and nutritional abnormalities; and (7) a copy of a current medication history, including any CYP3A4 inhibitors and/or CYP3A4 inducers; and (8) a copy of a sweat chloride result; and (9) height and weight measurements at the time of application; and (10) a baseline measurement of the number of days of CF-related hospitalisation (including hospital-in-the home) in the previous 12 months.
Administrative Advice	Special Pricing Arrangements apply. No increase in the maximum number of repeats may be authorised.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
IVACAFTOR				
Granule 50 mg	56	5	$[redacted]*	Kalydeco® Vertex Pharmaceuticals
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Tablet 150 mg	56	5	$[redacted]	

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	☒Medical Practitioners
Condition:	Cystic Fibrosis
PBS Indication:	Cystic Fibrosis
Treatment phase:	Continuing treatment
Restriction Level / Method:	☒Authority Required - In Writing
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 received PBS-subsidised initial therapy with ivacaftor, given concomitantly with standard therapy, for this condition, 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:	<age, and treatment restrictions as per initial criteria above> 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) for patients 6 years of age or older, the result of a FEV1 measurement performed within one month prior to the date of application. Note: FEV1, must be measured in an accredited pulmonary function laboratory, with documented no acute infective exacerbation at the time FEV1 is measured; and (4) a copy of a current medication history, including any CYP3A4 inhibitors and/or CYP3A4 inducers; and (5) a recent sweat chloride result; and (6) height and weight measurements at the time of application; and (7) a measurement of number of days of CF-related hospitalisation (including hospital in the home) in the previous 6 months.
Administrative Advice	Special Pricing Arrangements apply. No increase in the maximum number of repeats may be authorised.

**Proposed price updated based on Pre-Sub-Committee response*

2.2 Each dose of ivacaftor granules (50 mg and 75 mg) should be mixed with one teaspoon (5 mL) applesauce or other appropriate food. The sponsor clarified that the mini-tablets are the same as the granule formulation requested in the submission (p2, pre-PBAC response).

2.3 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 would be anticipated to affect the cost-effectiveness of ivacaftor in clinical practice in this setting. The submission does not present an economic evaluation.

2.4 The pre-PBAC response (p2) claimed that the TGA did not use weight-based criteria in the approved indication for ivacaftor. The sponsor stated that restricting ivacaftor use to patients 8 kg or above was clinically inappropriate as children under 8 kg may be malnourished and therefore may benefit most from ivacaftor treatment. However, the PBAC noted this claim maybe inconsistent with the approved consumer information, which states "do not give KALYDECO to children weighing less than 10 kg or under 2 years of age", due to lack of data on safety and effectiveness of this medicine.

2.5 Although an economic evaluation is not presented, the requested basis for listing is the same as that presented for prior submissions; cost-effectiveness compared with the nominated comparator, best supportive care (BSC).

3 Background

3.1 **TGA status at time of PBAC consideration:** ivacaftor granules were TGA registered on 9 September 2016 for the treatment of CF in patients aged 2 years and older who have a G551D or other gating (class III) mutation in the CFTR gene.

3.2 Monotherapy with ivacaftor 150 mg tablets for the treatment of CF patients aged 6 years and above who have a G551D mutation or other gating (class III) mutation in the CFTR gene has been considered by the PBAC on 5 previous occasions: major submissions in July 2013 and March 2014; and minor submissions in November 2014, July 2015, and November 2015. The PBAC recommended listing of ivacaftor tablets for this indication at its March 2014 meeting.

4 Clinical place for the proposed therapy

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

4.2 The submission proposed that ivacaftor will be administered in addition to current BSC to all patients aged 2 years and older who have a G551D or other gating (class III) mutation in the CFTR gene. The treatment would be ongoing under a weight-based dose regimen (until the patient reaches 25 kg) when the patient can move to a fixed dose regimen of 150 mg twice daily.

4.3 The PBAC noted that the proposed clinical place in therapy was in line with the TGA indication, which was only for children over 2 years. However, given that the submission argued that earlier commencement of treatment would improve outcomes, the PBAC questioned the rationale for delaying treatment until 2 years of age as most patients would be diagnosed with CF through newborn screening.

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

5 Comparator

5.1 The nominated comparator was BSC. This is the appropriate comparator.

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 (186), health care professionals (3) and organisations (1) via the Consumer Comments facility on the PBS website. The comments demonstrated strong support for access to subsidised ivacaftor treatment for certain CF patients at a younger age.

6.3 The PBAC noted the advice received from Cystic Fibrosis Australia highlighting the safety and efficacy of ivacaftor and the potential for improved health outcomes associated with commencing treatment with ivacaftor for certain CF patients at a younger age.

Clinical trials

6.4 The submission is based on one 24 week open label trial evaluating the safety and efficacy of ivacaftor granules 50 mg and 75 mg (KIWI Part B) (N=34) and an 84 week open-label extension of that study (KLIMB) (N=33). There were no head-to-head randomised trials available comparing ivacaftor + BSC with BSC. Supportive evidence from three placebo-controlled randomised trials (STRIVE, ENVISION and KONNECTION) was also presented.

6.5 Details of the trials presented in the submission are provided in the table below.

Table 1: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Nonrandomised trials		
Study 108 (KIWI)	A Phase 3, 2-Part, Open-Label Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Ivacaftor in Subjects With Cystic Fibrosis Who Are 2 Through 5 Years of Age and Have a CFTR Gating Mutation.	Vertex Pharmaceuticals. Internal Study Report. 19 Aug 2014
	Davies, J. C., S. Cunningham, W. T. Harris, A. Lapey, W. E. Regelmann, G. S. Sawicki, K. W. Southern, S. Robertson, Y. Green, J. Cooke and M. Rosenfeld. Safety, pharmacokinetics, and pharmacodynamics of ivacaftor in patients aged 2-years with cystic fibrosis and a CFTR gating mutation (KIWI): An open-label, single-arm study.	The Lancet Respiratory Medicine. 2016; 4(2): 107-115.
	Davies, J. C., S. Robertson, Y. Green, M. Rosenfeld and K. s. g. T (2014). "An open-label study of the safety, pharmacokinetics, and pharmacodynamics of ivacaftor in patients aged 2 to 5 years with cf and a CFTR gating mutation: the kiwi study."	Pediatric Pulmonology 49: 286
Study 109 (KLIMB)	A Phase 3, 2-Arm, Roll-Over Study to Evaluate the Long-term Safety and Pharmacodynamics of Ivacaftor Treatment in Pediatric Subjects With Cystic Fibrosis and a CFTR Gating Mutation	Vertex Pharmaceuticals. Internal Study Report. 29 Apr 2016
	Davies, J. C., S. Cunningham, K. W. Southern, S. Robertson, Y. Green, J. Cooke, M. Higgins and M. Rosenfeld (2015). "Ivacaftor treatment in preschool children with cystic fibrosis and a CFTR gating mutation: Extended evaluation".	Thorax 70: A14-A15
	Rosenfeld, M., S. Robertson, Y. Green, J. Cooke, A. Lawal, M. Higgins, J. Davies and G. Kiwi Study (2015). "Extended evaluation of ivacaftor treatment in pediatric patients with cystic fibrosis and a CFTR gating mutation".	Pediatric Pulmonology 50: 284-285

Source: Table B.2-2 p32 of the submission.

6.6 The key features of the non-randomised trials are summarised in the table below.

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Ivacaftor + BSC					
KIWI	34	OL, MC, single arm, 2-part study Part A: 4 days Part B: 24 weeks	High	Aged 2 to 5 years with CF with a CFTR gating mutation on at least one allele.	Absolute change in sweat chloride, weight, BMI, stature, weight-for-age z-score; BMI-for-age z-score, stature-for-age z-score, ppFEV1, and pulmonary exacerbations
KLIMB	33	OL, MC, single arm 84 weeks	High	Aged 2 to 5 years with CF with a CFTR gating mutation on at least one allele.	Absolute change in sweat chloride, weight, BMI, stature, weight-for-age z-score; BMI-for-age z-score, stature-for-age z-score, ppFEV1, and pulmonary exacerbations

Abbreviations: BMI, body mass index; CF, cystic fibrosis; CFTR, CF transmembrane conductance regulator gene; MC, multi-centre; OL, open label; ppFEV1, percent predicted forced expiratory volume in 1 second.
Source: compiled during the evaluation

6.7 The following issues were identified with regards to the study design:

- KIWI and KLIMB were non-randomised open label trials. These studies are designed to demonstrate the safety, pharmacokinetics and pharmacodynamics of ivacaftor in children aged 2 to 5 years. The overall risk of bias for the trials was high. However, the key efficacy outcomes are objective measures, and sweat chloride, weight, stature and FEV1 were based on objective laboratory analyses. Treatment with ivacaftor granules in the trials was based on the weight of the child. Safety was the primary outcome for both trials, and the safety populations were used as the basis of analysis.
- Missing data were not imputed and the sample size was small. The average responses reported in these trials were susceptible to outliers.
- The absence of a comparator group means it is not possible to assess the comparative safety/efficacy outcomes for ivacaftor in this patient group.

6.8 The TGA Clinical Evaluation Report noted that for the KIWI and KLIMB studies "efficacy was a tertiary endpoint and the study was not powered to reveal significant changes in these variables. The interpretation of data in relation to anthropometry, spirometry, clinical outcomes, microbiology, faecal elastase and immunoreactive trypsin is limited due to the lack of placebo arm, small sample size, short duration, and sensitivity of the measures… The limited findings in terms of lung function are not surprising, as spirometry is typically 'normal' in this age group and is a blunt measure of lung function… The evaluator does not accept the hypothesis the sponsor has made that early intervention in CF will improve long term outcomes."

Comparative effectiveness

6.9 A summary of the effectiveness for ivacaftor in patients aged 2 to 5 compared with patients aged 6 years and older is presented in Table 3.

Table 3: Summary of results of efficacy outcomes across the trials

Age group	2 – 5 years		≥ 6 years				
Study ID	**KIWI**	**KLIMB**	**ENVISION/ PERSIST**		**STRIVE/ PERSIST**		**KONNECTION**
Mean change (SD) from baseline	**24wks**	**108wks[a]**	**24 week**	**144wks[b]**	**24wks**	**144wks[b]**	**24wks**
	Pooled N=34	**Pooled N=33**	**150 mg N=52**	**150 mg N=25**	**150 mg N=161**	**150 mg N=72**	**150 mg N=39**
$ppFEV_1$ (% points)	1.8 (17.81)	11.9 (19.5)	10.67[c]	10.30 (12.4)[d]	10.13[c]	9.40 (10.8)[d]	NR
Sweat chloride (mmol/L)	-46.9 (26.19)	-54.7 (26.0)	-58.6[c]	NR	-52.2[c]	NR	-59.2[c]
BMI-for-age z-score (units)	0.37 (0.42)	0.27 (0.64)	0.33[c]	NR	0.36[c]	NR	0.42[c]
BMI (kg/m^2)	0.32 (0.54)	0.14 (0.97)	1.03[e]	2.5 (1.6)[d]	0.91[f]	1.2 (2.2)[d]	NR
Weight-for-age z-score (units)	0.20 (0.25)	0.20 (0.62)	0.30[c]	NR	0.33[c]	NR	0.41[c]
Weight (kg)	1.4 (0.56)	5.1 (1.8)	3.69[e]	14.8 (5.7)[d]	3.11[f]	4.1 (7.1)[d]	NR

Source: Commentary Table B(ii).6.2; N shown is for total sample size enrolled and may not reflect the number of patients evaluable for each endpoint.

Abbreviations: BMI, body mass index; NR, not reported; ppFEV1, percent predicted forced expiratory volume in 1 second; SD, standard deviation.

a Study duration of KLIMB is 84 weeks. Results are reported as Week 84, absolute change from KIWI baseline (~24weeks)

b Results are 144 weeks for patient enrolled in ENVISION and STRIVE that continued open-label extension study PERSIST

c Data cannot be verified. Submission source reported is 'Vertex Pharmaceuticals data on file'.

d Ivacaftor commentary 2014 Table B.6.1, 7.6.COM.21

e Week 24-data, n=26 [LS mean absolute change from baseline, FAS, linear mixed model]

f Week 48-data, n=83 [LS mean absolute change from baseline, FAS, linear mixed model]

6.10 The results from KIWI and KLIMB show treatment with ivacaftor resulted in a statistically significant improvement from baseline in the following outcomes:

- Absolute change in sweat chloride at 24 weeks (-46.9 mmol/L, p<0.0001) and 108 weeks (-54.7 mmol/L, p<0.0001). The difference is more than a 30% change from baseline. The National Health Service (NHS) criterion for response to treatment based on sweat chloride is a decrease in sweat chloride test to below 60 mmol/L or by at least 30%.
- Absolute change in weight at 24 weeks (1.4 kg, p<.0001) and 108 weeks (5.1 kg, p<0.0001). Under the [redacted]
- Ivacaftor therapy resulted in an improvement in the absolute change of ppFEV1 at week 24 (1.8 %, 95%CI: -6.6, 10.1; p=0.6588, n=20), that achieved statistical significance by week 108 (11.9%; 95% CI: 3.7, 20.1; p=0.008, n =16) compared with baseline. The PBAC has previously accepted that "the demonstrated 10% improvement in FEV1 over a period of up to 2 years is clinically significant and important" (p12, Ivacaftor PSD, November 2013 PBAC meeting).

6.11 The benefits of treatment with ivacaftor should be interpreted with caution due to the small sample size of the clinical studies, potential for confounding due to differences in background CF management, and the lack of comparable placebo control group.

6.12 Change in sweat chloride was presented as one of the main clinical outcomes. However, the submission has maintained the same claim as the March 2014 submission for ivacaftor tablets for patients aged 6 years and over, that sweat chloride is not a useful marker of clinical response to ivacaftor. At that time, sweat chloride was considered as a possible basis for a continuation rule. The pre- PBAC response stated that "…day 15 sweat chloride tests show poor sensitivity and specificity relative to week 48 FEV1 in the phase III clinical trials, hence … the application of such a continuation rule does not improve cost-effectiveness. This was confirmed in the published analyses by Seliger et al, 2013, which indicated poor negative predictive value (NPV) of day 15 sweat chloride relative to week 16 FEV1 responses, calculated by post-hoc analyses of the STRIVE and ENVISION data. This was despite a relatively encouraging positive predictive value (PPV)." The March 2014 pre-PBAC response also described the experience with sweat chloride testing in the UK, noting that "…sweat chloride decreased significantly at 2 months (median 114–51 mmol/L, p<0.001). This improvement was not correlated in absolute or relative terms with improvements in spirometry or BMI. More importantly for the individual patients concerned, the initial sweat chloride responses did not meet the pre-specified criteria at 2 months in four subjects, two of whom did meet criteria on repeat testing." The March 2014 pre-PBAC response also noted issues of intra-patient variability in sweat chloride results and practical challenges in accessing a limited number of laboratories able to perform testing.

6.13 As a result of the Committee's deliberations in March 2014, sweat chloride was not included as a clinical criterion to access PBS-subsidised ivacaftor. Although sweat chloride results are collected as part of the Authority application process, the absence of a result does not lead to rejection of the application. The PBAC recalled that they previously considered that sweat chloride was the most objective measure available, although its reliability as a marker for treatment response was not known.

Comparative harms

6.14 The submission did not present a comparison of safety outcomes for ivacaftor + BSC versus BSC.

6.15 A summary of the adverse events for ivacaftor is presented below.

Table 4: Summary of adverse events in KIWI and KLIMB, safety set

Study ID	KIWI (24 weeks)	KLIMB (84 weeks[a])
Patients, n (%)	**Pooled N=34**	**Pooled N=33**
Any AEs	33 (97.1)	33 (100.0)
Related AEs	11 (32.4)	9 (27.3)
AEs leading to death	0	0
SAEs	6 (17.6)	11 (33.3)
Related SAEs	1 (2.9)	2 (6.1)
AEs leading to study drug interruption	11 (32.4)	8 (24.2)
Related AEs leading to study drug interruption	2 (5.9)	3 (9.1)
AEs leading to study drug withdrawal	1 (2.9)	1 (3.0)
Related AEs leading to study drug withdrawal	1 (2.9)	1 (3.0)

Abbreviations: AE, adverse event; SAE, serious adverse event.
Source: Commentary Table B(ii).6.4
a Only AEs reported during the conduct of KLIMB are reported in this table.

Benefits/harms

6.16 A summary of the comparative benefits and harms for ivacaftor + BSC versus BSC is presented in the table below.

Table 5: Summary of comparative benefits and harms for ivacaftor + BSC and BSC

Benefits							
	Ivacaftor			**BSC**			**Mean difference*: ivacaftor vs. BSC (95% CI)**
	n	**Mean Δ baseline**	**SD**	**n**	**Mean Δ baseline**	**SD**	
$ppFEV_1$: absolute change from baseline							
KIWI	20	1.8	17.8	NA	NA	NA	NE
KLIMB	16	11.9	19.5	NA	NA	NA	NE
sweat chloride: absolute change from baseline							
KIWI	25	-46.9	26.2	NA	NA	NA	NE
KLIMB	23	-54.7	26.0	NA	NA	NA	NE
weight: absolute change from baseline							
KIWI	33	1.4	0.56	NA	NA	NA	NE
KLIMB	28	5.1	1.8	NA	NA	NA	NE

Harms						
	Ivacaftor	**BSC**	**RR (95% CI)**	**Event rate/100 patients***		**RD (95% CI)**
				Ivacaftor	**BSC**	
Patients with related AEs						
KIWI	11/34	NA	NE	32.4	NA	NE
KLIMB	9/33	NA	NE	27.3	NA	NE
Patients with any SAEs						
KIWI	6/34	NA	NE	17.6	NA	NE
KLIMB	11/33	NA	NE	33.3	NA	NE
Patients with AEs leading to study drug interruption						
KIWI	11/34	NA	NE	32.4	NA	NE
KLIMB	8/33	NA	NE	24.2	NA	NE

Abbreviations: AE, adverse event; BSC, best supportive care; CI, confidence interval; NA, not applicable; NE, not estimable; ppFEV1, percent predicted forced expiratory volume in 1 second; RD, risk difference; RR, risk ratio; SAE, serious adverse event; SD, standard deviation;
Source: Compiled during the evaluation
* Duration of exposure: KIWI = 24 weeks; KLIMB = 84 weeks

6.17 The difference in benefits and adverse events between ivacaftor and BSC in patients aged 2 to 5 years is unknown.

Clinical claim

6.18 The submission described ivacaftor as similar in terms of comparative effectiveness and safety in patients aged from 2 to 5 years compared with patients aged 6 years and older. The PBAC noted that no data comparing ivacaftor to the nominated comparator of BSC were provided.

6.19 Previous submissions in patients aged 6 years and older with CF and a G551D mutation (July 2013; March 2014) have described ivacaftor as superior in terms of comparative effectiveness and equivalent in terms of comparative safety over BSC.

6.20 The clinical claim regarding efficacy may be reasonable for the outcomes of weight gain, ppFEV1, and reduction in sweat chloride over 108 weeks. However, the following issues were considered by the PBAC:

- The key trials presented in the submission (KIWI and KLIMB) are non-randomised, single arm and open label. As such, the trials were subject to considerable bias and the effectiveness estimates were subject to considerable uncertainty.
- The PBAC noted the change in sweat chloride associated with ivacaftor for patients aged 2 to 5 years was similar to that for patients aged 6 years and older. However, the PBAC noted that the sponsor has previously argued that sweat chloride is not correlated with response to ivacaftor treatment (see paragraph 6.12). The TGA evaluator concluded that the effects of ivacaftor on sweat chloride are similar to that seen in older children and adults (TGA Clinical Evaluation Report, p15), however did not assess whether the extrapolation of efficacy from adults to children was appropriate.
- The PBAC noted an increase in weight among patients aged 2 to 5 years treated with ivacaftor. This potentially indicated benefit from the early treatment, particularly as malnutrition is a common problem in this age group. The PBAC also noted that the average weight gain observed was higher than the average weight gain for children of this age (approximately 2 kg per year). However, the PBAC considered that assessment of this outcome was problematic without a comparable placebo group.
- The effect of ivacaftor on ppFEV1 is most relevant to the claim of comparable efficacy as this outcome is the best predictor of mortality. The PBAC noted that an increase in ppFEV1 of over 10 percentage points was observed at 108 weeks for the 2 to 5 years age group, whereas a similar increase occurred at 24 weeks in patients 6 years and older. The PBAC noted the comparatively slower improvement in ppFEV1 in the patients aged 2 to 5 compared with the older patients. The PBAC also noted the difficulty in obtaining accurate measurements of ppFEV1 in children aged 2 to 5 years. The PBAC considered that the gradual increase in ppFEV1 could be due to an improvement in the patient's ability to perform the test over time, and that interpretation of this outcome is therefore difficult without a comparator arm.
- The PBAC noted that efficacy was assessed in terms of intermediate outcomes, and collected over a short period of time, but that ivacaftor may be used as a lifelong treatment. The PBAC previously considered that in children over 6 years, the clinical claim was supported out to 144 weeks based on the PERSIST

extension study, but remained unconvinced that the clinical claim was supported beyond 144 weeks (Section 9 p6, Ivacaftor PSD March 2014). The results presented from KIWI and KLIMB are for a maximum of 108 weeks of treatment.

6.21 The PBAC considered that the clinical claim as presented in the submission appears to be reasonable with respect to safety. The PBAC previously accepted the claim of equivalent safety was supported in the short term but noted the long term safety of ivacaftor is unknown (Section 9 p4, Ivacaftor PSD July 2013). The PBAC noted that the tolerability of ivacaftor in patients 2 to 5 years appears to be similar to that in older patients. One withdrawal of ivacaftor treatment due to adverse events was reported in each of the KIWI and KLIMBtrials.

6.22 The PBAC considered that the evidence to support both the efficacy and safety of the ivacaftor treatment in patients aged 2 to 5 years was limited by the lack of a control group, but also noted the ethical difficulties associated with such an approach. Notwithstanding, the PBAC considered that on the basis of the aetiology of CF and evidence of similar response in patients aged 2 to 5 years compared to older patients, that it was biologically plausible that earlier treatment would confer some benefit to patients, however the magnitude of any incremental benefit in the short term and over the lifetime of the patient was unknown.

6.23 The PBAC considered that the claim of similar effectiveness to treatment in patients over 6 years was plausible but not established. The PBAC noted that no claim was made with respect to the nominated comparator (BSC). However, the PBAC recalled that they had previously accepted that ivacaftor had superior efficacy over BSC in patients over the age of 6 years and considered that it was plausible that this claim could be reasonably extrapolated to patients aged 2 to 5 years. Similarly, the PBAC considered that it was plausible that the safety claim for ivacaftor over BSC in patients over the age of 6 years as previously accepted by the PBAC could be extrapolated to patients aged 2 to 5 years.

Economic analysis

6.24 The submission did not present an economic evaluation and claimed that as the PBAC previously considered the cost effectiveness of ivacaftor in patients over 6 years of age was acceptable with [redacted] that this could be extrapolated to patients aged 2 to 5 years, and a separate economic evaluation was not required to demonstrate cost-effectiveness in the proposed population.

6.25 The PBAC considered that this approach was inappropriate because [redacted] there would be additional PBS expenditure for the treatment of children aged 2 to 5 years, and it should be assessed if the additional expenditure is cost-effective. Specifically, the extension of the ivacaftor indication to include patients aged 2 to 5 years would potentially add an additional four years of treatment for each patient, and the associated additional cost to the PBS would be $[redacted] (DPMQ).

6.26 The PBAC noted it was implicitly assumed that only the PBS budget for ivacaftor would be impacted by the requested extension of the existing PBS listing. This is not the case. Paediatric patients treated with ivacaftor require ophthalmological

consultations and increased monitoring for potential hepatotoxicity associated with treatment. These costs would be incurred through the MBS and privately to patients, and should be included in an assessment of the cost-effectiveness of ivacaftor for this population.

6.27 The PBAC considered that as the incremental benefit of starting ivacaftor treatment at a younger age was unknown and difficult to demonstrate (see paragraph 6.19), the cost-effectiveness of the additional years of treatment was highly uncertain. The PBAC noted that the intention of the submission [redacted]. However, the PBAC was of the view that it would be possible to negotiate an alternative arrangement whereby the intended outcome could be achieved.

Drug cost/patient/year: $[redacted].

6.28 The requested price for the 50 mg and 75 mg ivacaftor granules was the same (AEMP $[redacted] per pack which provides 28 days of treatment). The submission did not provide an estimate of the number of packs used per year. Assuming 13 packs per patient per year are dispensed the cost would be $[redacted] per patient per year. Treatment is ongoing for the lifetime of the patient.

6.29 The price per milligram for each formulation and strength differs ($[redacted] for the 150 mg tablet, $[redacted] for the 75 mg granules, $[redacted] for the 50 mg granules). The PBAC noted that the submission did not justify the higher price per mg for the ivacaftor granules compared with the tablets.

6.30 The PBAC further noted that the proposed restriction enabled patients over the age of 6 years and/or 25 kg to use the ivacaftor granules. This was appropriate from an equity perspective, as some patients over 25 kg may have difficulty swallowing the tablets. However, the PBAC noted that if a patient over 25 kg used the granules instead of the tablets, the cost of treatment would be doubled for that patient. The PBAC considered that in the event of listing it would be appropriate for all patients to have access to the granules, but that this should not result in a higher treatment cost.

Estimated PBS usage & financial implications

6.31 The submission did not present financial estimates of extending the listing of ivacaftor on the PBS on the assumption that there would be [redacted] to the PBS as a result of the current risk share arrangement. As discussed in paragraph 6.27, the PBAC did not agree with this assumption in the circumstances where the [redacted] were not reached. Based on the submission's assumption of less than 10,000 additional patients per year, the listing would be expected to cost up to $30 - $60 million over the first five years of listing if the [redacted] have not been reached.

6.32 The submission did not address uncertainties associated with the extent of dose reduction due to hepatic impairment or treatment adherence. The costs of monitoring patients, including liver function tests and ophthalmologic examination, were not considered. The submission also did not include costs associated with patients over

25 kg using the granules, which would incur a greater cost to the PBS than the tablets at the currently proposed price.

6.33 This submission was not considered by DUSC. The submission adopted an epidemiological approach in estimating patient numbers.

Table 6: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated					
Market share	%	%	%	%	%
No. of patients					

Source: Section E of the submission.

6.34 The submission's estimate that less than 10,000 patients aged 2 to 5 years will be treated each year with ivacaftor granules may be an underestimate. In the second and subsequent years, patients who commenced ivacaftor granules in year 1 and who have not moved onto ivacaftor tablets will be joined by newly diagnosed patients. 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.

Financial Management –

6.35 The submission also proposed that the are not applicable in patients aged 2 to 5 years,

6.36 The PBAC considered that on the basis of unclear effectiveness in the 2 to 5 year age group and the limited reliable evidence that could be collected in patients commencing ivacaftor before the age of 6, The PBAC also noted that as CF is mostly diagnosed in newborn screening, most patients would initiate when in the 2 to 5 year age group,

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

7 PBAC Outcome

7.1 The PBAC deferred making a recommendation on the listing of ivacaftor granules for treatment of CF who have a G551D mutation or other class III gating mutations in the CFTR gene to include patients aged 2 to 5 years to allow for further negotiation with the sponsor. The PBAC considered that this was necessary as the incremental benefit of commencing treatment at a younger age, and consequently the cost-effectiveness, was unclear and further negotiation was required to [redacted]

7.2 The PBAC acknowledged the consumer comments received from carers of patients with CF, health care professionals and patient organisations that indicated strong support for access to treatment with ivacaftor for certain CF patients at a younger age.

7.3 The PBAC accepted the clinical place for ivacaftor as an add-on to current BSC for patients aged 2 to 5 years and considered that BSC was the appropriate comparator.

7.4 The PBAC noted that the submission was based on one 24 week open label trial with a small sample size which evaluated the safety and efficacy of ivacaftor granules 50 mg and 75 mg (KIWI Part B) and an 84 week open-label extension of that study (KLIMB). The PBAC noted that no data comparing ivacaftor to the nominated comparator were provided. Instead the submission sought to extrapolate the previously demonstrated efficacy of ivacaftor in patients aged 6 years and over by showing comparability in response measures between these patients and patients aged 2 to 5 years. Overall, the PBAC considered that the claim of superior efficacy over BSC in patients aged 2 to 5 years was biologically plausible. However, the PBAC considered that the extent of benefit of commencing treatment with ivacaftor at a younger age had not been assessed and was therefore unknown.

7.5 The PBAC noted that the tolerability of ivacaftor in patients 2 to 5 years is similar to older patients.

7.6 The PBAC did not accept the submission's claim that the cost-effectiveness demonstrated for patients aged over 6 years could be extrapolated to patients aged 2 to 5 years. The PBAC considered that as the incremental benefit of commencing treatment with ivacaftor earlier was unknown, the cost-effectiveness of such treatment was highly uncertain.

7.7 The PBAC considered that the intention of the submission [redacted], given the difficulty in demonstrating the incremental benefit and therefore cost-effectiveness of earlier treatment with ivacaftor. However, the PBAC did not agree with the submission's claim [redacted] The PBAC was of the view that it would be possible to negotiate an

alternative arrangement [redacted].

7.8 The PBAC also considered that due [redacted]. The PBAC did not consider that the approach proposed by the sponsor would adequately address this issue. The PBAC considered that it may be appropriate [redacted]

7.9 The PBAC noted that some patients over 25kg may wish to use the ivacaftor granules, and that at the current proposed price the cost of treating these patients would be doubled compared to the tablets. The PBAC considered that in the event of listing it would be appropriate from an equity and quality use of medicines perspective for all patients to have access to the granules, but that the cost of treatment per patient should not be any higher as a result.

7.10 The PBAC noted that based on the submission's assumption of less than 10,000 additional patients per year, the cost to the PBS over the first five years of listing could be up to $30 - $60 million above current expenditure if the caps have not been reached.

Outcome:
Deferred

8 Context for Decision

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

9 Sponsor's Comment

The sponsor had no comment.

Addendum:

CHANGES TO PRESENT (OR RECOMMENDED) PBS AVAILABILITY

When the PBAC makes a recommendation under section 101(3) of the *National Health Act 1953* ("the Act") in relation to a drug/medicinal preparation which it considers should be made available as a pharmaceutical benefit under Part VII of the Act, it is also required to consider whether the drug/medicinal preparation should be made available only in certain circumstances (see section 101(3C) of the Act). Where the PBAC considers that the drug/medicinal preparation should be made available only in certain circumstances, it specifies the circumstances in its recommendation under section 101(3).

At its meeting on **25 January 2017**, the PBAC in making its recommendation under section 101(3) of the Act, decided to recommend a change to the circumstances under which ivacaftor is made available as a pharmaceutical benefit under Part VII of the Act.

A note of the PBAC's decision follows.

IVACAFTOR,
granules, 50 mg and 75 mg sachets,
Kalydeco®,
Vertex Pharmaceuticals Pty Ltd.

Subsequent to the November 2016 PBAC meeting, the PBAC considered at the January 2017 extraordinary meeting, additional information provided by the sponsor in relation to the effectiveness, cost-effectiveness and financial impact of extending the listing of ivacaftor to include patients aged 2-5 years.

The PBAC recommended the Section 100 (Highly Specialised Drugs Program), Authority Required listing of a new presentation of ivacaftor, in the form of granules, for treatment of CF in patients aged 2 years or over who have a G551D mutation or other class III gating mutations in the CFTR gene.

The PBAC noted the additional data from the Ivacaftor Long Term Safety Study using United States (US) CF registry showed a statistically significant reduction in the risk of hospitalisation in patients aged <6 years who were treated with ivacaftor compared with matched controls who did not receive ivacaftor (RR 0.68, 95%CI: 0.49-0.95). There was also a reduction in pulmonary exacerbations for patients <6 years treated with ivacaftor (0.68, 95%CI: 0.45-1.04).The reduction was not statistically significant but this may have been due to the small sample size. The PBAC also noted a *post hoc* analysis of the treatment difference (ivacaftor versus placebo) for change from baseline in FEV_1 from the ENVISION RCT for patients indicated similar FEV_1 responses in the 6-8 year age group compared with the older age groups, further supporting that the efficacy of ivacaftor is independent of age.

The PBAC noted that limited data in the 2-5 years age group were provided. However, the PBAC also noted the ethical difficulties associated with undertaking clinical trials in this setting. The PBAC recalled their earlier advice that the claim of superior efficacy over BSC in patients aged 2 to 5 years was biologically plausible, and considered that in this situation, the data provided were sufficient to support this claim.

The PBAC noted the cost-effectiveness analysis newly provided by the sponsor 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).

The PBAC recalled that [redacted] The PBAC considered that the [redacted]

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. The PBAC also noted that the sponsor indicated a willingness to ensure that this was the case.

The PBAC recommended that, as proposed by the sponsor, [redacted] The PBAC noted that [redacted], the listing would result in an estimated cost to the PBS of $20 - $30 million over the first five years of listing. However, the PBAC noted that this estimate did not take into account any increase in the number of treated patients over the age of 6 years, or any renegotiation of the RSA when it expires.

The PBAC also recommended that the extension to the listing to include patients aged 2-5 years be flowed-on to the ivacaftor tablet form.

The PBAC considered that it was not necessary to include a minimum weight in the restriction, and noted that the grandfather restriction for the ivacaftor 150mg tablets could be removed as all patients should have now been moved on to PBS treatment.

Outcome:
Recommended

Recommended listing

Add new item (ivacaftor granules): restriction to be finalised
Amend existing listing as follows (ivacaftor tablets): restriction to be finalised