5.08 IVACAFTOR, Sachet containing granules 25 mg, Sachet containing granules 50 mg, Sachet containing granules 75 mg, Tablet 150 mg, Kalydeco®, VERTEX PHARMACEUTICALS (AUSTRALIA) PTY. LTD.

1 Purpose of submission

1.1 The Category 2 submission requested a Section 100-Highly Specialised Drugs Program, Authority Required listing for ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 4 months and older who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data. This includes the following additional populations:

- CF patients aged 4 months to less than 12 months of age with a gating (Class III) mutation in the CFTR gene on at least one allele (referred to in the submission as the gating population).
- CF patients aged 4 months and older with an R117H mutation in the CFTR gene on at least one allele;
- CF patients aged 4 months and older with a non-splice residual function (RF) mutation in the CFTR gene on at least one allele; and
- CF patients aged 4 months and older with other mutations in the CFTR gene that are responsive to ivacaftor based on clinical and/or in vitro assay data in Fischer Rat Thyroid (FRT) cells indicating that ivacaftor increases chloride transport to at least 10% over baseline (referred to in the submission collectively as IVA-responsive rare mutations)

1.2 Listing was pragmatically requested on an age-based (gating population), rarity-based (RF and IVA-responsive rare mutations) and clinical need (R117H mutations) equity argument; no economic evaluation was presented in the submission to support the listing requested in any of the proposed populations.

1.3 The key components of the listing as presented by the submission are provided in Table 1.

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

Component	Description
Population	CF patients aged 4 to less than 12 months of age with a gating (Class III) mutation in the CFTR gene on at least one allele CF patients aged 4 months or older with an R117H mutation in the CFTR gene on at least one allele CF patients aged 4 months or older with a non-splice RF mutation in the CFTR gene on at least one allele CF patients aged 4 months or older with other mutations in the CFTR gene that are responsive to ivacaftor based on clinical and/or in vitro assay data
Intervention	Ivacaftor (weight-based dosing as per the PI document)
Comparator	BSC alone
Outcomes	Absolute change from baseline in: $ppFEV_1$ (where relevant); sweat chloride; nutritional status (weight, length, weight-for-length z-scores, weight-for-length-for-age z-scores, and weight-for-length percentiles); FE-1; IRT. 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: Modified from unlabelled Table, p28 of the submission.
BSC = best supportive care; CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; FE-1 = faecal elastase-1; IRT = immunoreactive trypsinogen; IVA = ivacaftor; PI = product information; $ppFEV_1$ = percent predicted forced expiratory volume; RF = residual function.

2 Background

Registration status

2.1 The TGA indication for ivacaftor was expanded on 14 February 2023 to include the treatment of CF in patients aged 4 months 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 data.

Previous PBAC considerations

2.2 The Pharmaceutical Benefits Advisory Committee (PBAC) first considered ivacaftor for the treatment of CF in patients who have a G551D or other Class III gating mutation in the CFTR gene in 2013, with subsequent submissions expanding the PBS listing to lower the starting age of treatment to 12 months of age (ivacaftor Public Summary Documents (PSDs), November 2013, November 2014, November 2016, March 2019 PBAC meetings).

2.3 The PBAC has also previously considered tezacaftor/ivacaftor (TEZ/IVA) for the treatment of CF in patients aged 12 years and older who have at least one non-splice RF mutation in the CFTR gene (TEZ/IVA PSD, November 2019 PBAC meeting) and elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) for the treatment of CF in patients aged 6 years and older who have at least one F508del mutation in the CFTR gene (F/any) (ELX/TEZ/IVA PSD, November 2022 PBAC meeting with March 2023 addendum).

2.4 The PBAC has previously considered lumacaftor/ivacaftor (LUM/IVA) and TEZ/IVA for the treatment of CF in patients homozygous for the F508del mutation in the CFTR gene (F/F), aged 1 year and older and 12 years and older respectively (LUM/IVA PSD, July

2023 PBAC meeting and TEZ/IVA PSD, March 2019 PBAC meeting). LUM/IVA and TEZ/IVA for F/F mutation patients was not relevant to this submission.

2.5 A summary of current and proposed PBS listings for ivacaftor, whether alone or in combination with other CFTR modulators, for the patient populations presented in this submission is shown in Table 2.

Table 2: Current and proposed PBS listings for ivacaftor in CF patient populations presented in this submission (orange shading are new populations, blue shading is PBS listed populations),

Age	Gating population		R117H population		RF population		Other	
	F	non-F	F	non-F	F	non-F	F	non-F
4 months < 1 year	IVA	IVA	IVA	IVA	IVA	IVA	IVA	IVA
1 < 6 yrs	IVA	IVA						
6 <12 yrs	ELX/TEZ/IVA[1, 2]		ELX/TEZ/IVA[2]		ELX/TEZ/IVA[2]		ELX/TEZ/IVA[2]	
12 yrs +						TEZ/IVA		

Source: developed for the Commentary using information in Sections 1.2.1 and 1.2.2 of the submission.
ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; F = F508del mutation present in the CFTR gene on the other allele; IVA = ivacaftor; non-F = no F508del mutation present in the CFTR gene on the other allele; PBS = Pharmaceutical Benefits Scheme; TEZ/IVA = tezacaftor/ivacaftor.
1. IVA is PBS listed for this population
2. ELX/TEZ/IVA is currently being evaluated by the TGA for used in CF patients 2 to 5 years heterozygous for the F508del mutation

2.6 The proposed PBS listing provides access for the following additional patient populations:

- Gating population aged 4 months to 12 months (which represents 3% of the additional patient population in Year 1 of PBS listing);
- F/(R117H or RF) aged 4 months to 6 years (41%);
- non-F/RF aged 4 months to 12 years (7%);
- non-F/R117H aged 4 months and over (35%);
- F/in vitro responsive aged 4 months to 6 years (4%); and
- non-F/in vitro responsive aged 4 months and over (10%).

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, 25 mg granules, 4 x 14 sachets	Published (public): $21,375.00 Published (private): $21,423.37 Effective (public): $ [redacted] Effective (private): $ [redacted][a]	1	56	5	Kalydeco
IVACAFTOR, 50 mg granules, 4 x 14 sachets		1	56	5	Kalydeco
IVACAFTOR, 75 mg granules, 4 x 14 sachets		1	56	5	Kalydeco
IVACAFTOR, 150 mg film-coated tablets		1	56	5	Kalydeco

Category / Program: Section 100 – Highly Specialised Drugs Program
Prescriber type: ☒Medical Practitioners
Restriction Type – ☒Authority Required – non-immediate/delayed assessment by Services Australia
Indication: *Cystic fibrosis*
Treatment Phase: Initial treatment *and* Continuing treatment
~~**Treatment criteria:**~~
~~Must be treated by a specialist respiratory physician with expertise in cystic fibrosis or in consultation with a specialist respiratory physician with expertise in cystic fibrosis if attendance is not possible due to geographic isolation~~
~~**AND**~~
~~**Treatment criteria:**~~
~~Must be treated in a centre with expertise in cystic fibrosis or in consultation with a centre with expertise in cystic fibrosis if attendance is not possible due to geographic isolation~~
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 a sweat chloride value of at least 60 mmol/L by quantitative pilocarpine iontophoresis
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:
The treatment must be given concomitantly with standard therapy for this condition.
Clinical criteria:
Patient must not receive more than 24 weeks of treatment per treatment course authorised under this restriction
AND
Population criteria:
Patient must be aged 4 months 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
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.
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.
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 *the specific mutation considered to be responsive to ivacaftor as listed in the TGA approved PI* ~~G551D mutation or other gating (Class III)~~ mutation on the CFTR gene - quote each of the: (i) name of the pathology report provider, (ii) date of pathology report, (iii) 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.

Source: Table 1.4.1, p50 of the submission, Table 4.4.4, p218 of the submission; Unlabelled Table, pp51-52 of the submission.
CFTR = Cystic fibrosis transmembrane conductance regulator; IV = intravenous; PBS = Pharmaceutical Benefits Scheme.
[a] calculated during the evaluation as the public effective price plus the PBS ready dispensing fee and $40 mark-up.

3.2 The submission proposed a Special Pricing Arrangement (SPA) with published and effective prices.

3.3 The proposed restriction did not include the clinical criteria: 'Patient must have a sweat chloride value of at least 60 mmol/L by quantitative pilocarpine iontophoresis'. The pre-PBAC response stated inclusion of a clinical criterion for sweat chloride in the restriction is historical as ivacaftor was the first PBS listed CFTR modulator and the more recent restrictions for the other CFTR modulators do not include this criterion.

3.4 The submission proposed a combined restriction for initial and continuing treatment, while all currently listed CFTR modulators include a separate initial and continuing restriction. The current ivacaftor initial restriction requests prescribers provide (i) details of pathology report substantiating mutation and (ii) sweat chloride result. The continuing restrictions do not have such requirements. The proposed combined listing requires prescribers to provide this information with all authority applications.

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 Ivacaftor is a selective potentiator of the CFTR protein. In vitro, ivacaftor increases the open probability of the CFTR channel gate to enhance chloride transport. This has been demonstrated in normal CFTR and in CFTR mutations that have reduced channel-open probability, such as G551D and R117H. The exact mechanism leading ivacaftor to prolong the gating activity in other ivacaftor-responsive mutations has not been

completely elucidated. Treatment with ivacaftor is ongoing for the lifetime of the patient and is intended for use as an adjunct to therapies used as part of best supportive care (BSC).

4.3 The submission stated that for the gating population, the proposed clinical management algorithm is the same as that currently applied when patients are aged 12 months and older. This was appropriate.

4.4 The submission stated that patients with an F508del mutation (F) in the CFTR gene on the other allele will have access to ELX/TEZ/IVA from 6 years of age; it is expected that these patients will switch to ELX/TEZ/IVA from ivacaftor when eligible to do so as recommended by the European Cystic Fibrosis Society (ECFS) consensus guidelines[1]. This represents approximately 45% of the additional patient population. Additionally, patients with an identified non-splice RF mutation in the CFTR gene that is responsive to TEZ/IVA will be eligible for PBS-listed TEZ/IVA from 12 years of age; it is expected that these patients will switch from ivacaftor to TEZ/IVA when eligible to do so. This represents approximately 7% of the additional patient population. See Table 2 for further information.

5 Comparator

5.1 The submission nominated BSC as the main comparator. BSC in CF includes daily prophylactic medications and supplements such as pancreatic enzymes, nutritional and vitamin supplements, oral or nebulised antibiotics, nebulised mucolytic agents, anti-inflammatories, bronchodilators, and daily physiotherapy.

5.2 Given that treatment with ivacaftor is ongoing for the lifetime of the patient, the more appropriate comparison for the gating population is of early (4 months of age) versus later (1 year and over) commencement of treatment; this comparison was not addressed by the submission. Similarly, for patients who have a non-splice RF mutation or F508del mutation in the CFTR gene on the other allele, the more appropriate comparator for ivacaftor is TEZ/IVA from 12 years of age and ELX/TEZ/IVA from 6 years of age respectively; these comparisons were not addressed by the submission.

5.3 The Economic Sub-Committee (ESC) considered the more appropriate comparator in the proposed setting is that of later commencement of treatment but the submission did not compare the incremental benefit of commencing ivacaftor at 4 months with commencement of CFTR modulator(s) at a later age. The ESC acknowledged the difficulty of conducting a comparative analysis of different initiating ages (as discussed

[1] Southern, K. W*., et al.* (2023). Standards of care for CFTR variant-specific therapy (including modulators) for people with cystic fibrosis. *Journal of Cystic Fibrosis* 22(1): 17-30.

in the Pre-Sub-Committee Response (PSCR)); however, the uncertainty regarding the clinical benefit and cost-effectiveness of starting treatment early remains.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The sponsor discussed the current and future treatment landscape for CF. The sponsor noted that approximately 5% of patients with CF will not benefit from a CFTR modulator as they do not make CFTR protein. The sponsor presented two case studies that supported access to ivacaftor. The sponsor noted that patients who respond to ivacaftor will also respond to ELX/TEZ/IVA and clinical data supporting a broad listing for ELX/TEZ/IVA in patients with responsive mutations had recently become available.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (11), health care professionals (1) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described the effectiveness of CFTR modulators (including ivacaftor) to treat individuals with CF. Input described the importance of beginning CTFR modulation early in disease progression, and noted the positive impacts on pancreatic function, lung function, nutrition and growth, and quality of life observed in those being treated with ivacaftor. Comments noted the manageable safety profile of ivacaftor. Input described the current prohibitive cost of ivacaftor and other CFTR modulators and the importance of equity of access for individuals with rare mutations.

6.3 The PBAC noted and welcomed the input from Cystic Fibrosis Australia (CFA) and the National Paediatric Medicines Forum (NPMF). The CFA were supportive of extending the benefit from treatment with ivacaftor to more patients with CF. The CFA requested the PBAC consider extending the listing of ELX/TEZ/IVA to cover rarer mutations to further increase the number of patients that would benefit from treatment with CFTR modulators. The NPMF considered expanding the listing of ivacaftor would be beneficial to all paediatric CF patients with research supporting treatment from a young age to slow or prevent the irreversible progression of CF.

Clinical studies

6.4 The submission was based on evidence from the following studies:

- Gating population
  - Study 124, a single arm study that evaluated the safety and efficacy of ivacaftor granules in patients aged 4 to < 12 months with a gating (class III) mutation. This was a two-part study: Part A (n=12) evaluated safety and

pharmacokinetics (PK); Part B (n=17) evaluated safety, PK and pharmacodynamics (PD).

- R117H mutation:
  - Study 110, a randomised controlled trial (RCT; n=69) that evaluated the safety and efficacy of ivacaftor in patients with the R117H mutation aged ≥ 6 years.
  - Study 112, an open-label extension (OLE) study of patients from Study 110 who rolled over to Study 112 (n=121, Study 110 rollover patients, n=65; observation arm n=4). Results for the observation arm were not included in the submission.
  - Study 122, an observational study of patients with the R117H mutation aged ≥ 2 years that used the United States Cystic Fibrosis Foundation Patient Registry (US CFFPR) to evaluate the long-term efficacy of ivacaftor (n=369).
- Non-splice RF mutation:
  - Study 108, a RCT crossover study of CF patients aged ≥ 12 years who were heterozygous for the F508del-CFTR mutation and an RF mutation (n=248). Study 108 was previously considered by the PBAC as part of the March 2019 submission for TEZ/IVA seeking reimbursement for RF patients.
  - Study 113, a RCT crossover study of patients aged ≥ 12 years with CF with clinical or molecular evidence of an RF mutation (n=24).
  - Study 127, a RCT crossover study of patients with CF aged ≥ 6 years who have a 3849 + 10KB C→T or D1152H-CFTR mutation.
  - Study 128, a 3-year observational study of CF patients aged ≥ 2 years with CFTR mutations that are IVA-responsive based on in vitro and/or clinical evidence (n=349), using data from the US CFFPR.
  - The above studies were presented to provide evidence for the correlation of in vitro with in vivo response for non-splice RF mutations, but Study 108, 113 and 127 included patients who had a splice mutation which is not approved for use with ivacaftor[2].
- IVA-responsive rare mutations population (non-clinical studies):
  - Three non-clinical studies that evaluated the in vitro responsiveness of CFTR mutations to ivacaftor potentiation (Yu et al. (2012), Van Goor et al. (2014), and Report P289).

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

[2] Ivacaftor PI, https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/PICMI?OpenForm&t=&q=ivacaftor

Table 3: Studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Gating population		
Study 124 VX15-770-124	Clinical Study Report, Interim Analysis 2 and Interim Analysis 3 A Phase 3, 2-Part, Open-label Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Ivacaftor in Patients With Cystic Fibrosis Who Are Less Than 24 Months of Age at Treatment Initiation and Have a CFTR Gating Mutation	NCT02725567
R117H population		
Study 110 VX11-770-110	Clinical Study Report, March 2014: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Ivacaftor in Patients With Cystic Fibrosis Who Have the R117H CFTR Mutation	NCT01614457
	Moss RB, Flume PA, Elborn JS, Cooke J, Rowe SM, McColley SA, Rubenstein RC, Higgins M; VX11-770-110 (KONDUCT) Study Group Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation: a double-blind, randomised controlled trial.	Lancet Respir Med. 2015 Jul;3(7):524-33. doi: 10.1016/S2213-2600(15)00201-5. Epub 2015 Jun 9.
Study 112 VX12-770-112	Clinical Study Report, October 2016: A Phase 3, Two-Arm, Rollover Study to Evaluate the Safety of Long-Term Ivacaftor Treatment in Patients 6 Years of Age and Older with Cystic Fibrosis and a Non-G551D CFTR Mutation	NCT01707290
	Pilewski JM, De Boeck K, Nick JA, Tian S, DeSouza C, Higgins M, Moss RB. Long-Term Ivacaftor in People Aged 6 Years and Older with Cystic Fibrosis with Ivacaftor-Responsive Mutations.	Pulm Ther. 2020 Dec;6(2):303-313. doi: 10.1007/s41030-020-00129-2. Epub 2020 Sep 23.
Study 122 VX15-770-122	Clinical Study Report, December 2020: A Study in US Cystic Fibrosis Patients With the R117H-CFTR Mutation to Confirm the Long-term Safety and Effectiveness of Kalydeco, Including Patients <18 Years of Age, Combining Data Captured in the Cystic Fibrosis Foundation Patient Registry From an Interventional Cohort and a Non-interventional Cohort	NCT02722057
	Higgins M, Farietta T, Campbell D, Liu M, Ostrenga J, Elbert A, Shih J, Volkova N. Registry-based study in people with cystic fibrosis and an R117H variant treated with ivacaftor.	BMJ Open Respir Res. 2023 May;10(1):e001447. doi: 10.1136/bmjresp-2022-001447. PMID: 37230763.
Non-splice RF population		
Study 108 VX14-661-108	Clinical Study Report Study, June 2018: A phase 3 study to evaluate the efficacy and safety of ivacaftor and VX-661 in combination with ivacaftor in Patients aged 12 years and older with cystic fibrosis, heterozygous for the F508del-cystic fibrosis transmembrane conductance regulator (CFTR) mutation.	NCT02392234
	Rowe SM, Daines C, Ringshausen FC, Kerem E, Wilson J, Tullis E, Nair N, Simard C, Han L, Ingenito EP, McKee C, Lekstrom-Himes J, Davies JC. Tezacaftor-Ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis.	New England Journal of Medicine. 2017; 337(21): 2024–2035.
Study 113 VX12-770-113	Nick JA, St Clair C, Jones MC, Lan L, Higgins M; VX12-770-113 Study Team. Ivacaftor in cystic fibrosis with residual function: Lung function results from an N-of-1 study.	NCT01685801 J Cyst Fibros. 2020 Jan;19(1):91-98. doi: 10.1016/j.jcf.2019.09.013.
Study 127 VX16-770-127	Clinical Study Report, May 2019: A Randomized, Double-blind, Placebo-controlled, Crossover Study to Evaluate the Efficacy of Ivacaftor in Patients with Cystic Fibrosis Who are 6 Years of Age and Older and Have Either a 3849 + 10KB C→T or D1152H-CFTR Mutation	*NCT03068312*

Trial ID	Protocol title/ Publication title	Publication citation
	Kerem, E., Cohen-Cymberknoh, M., Tsabari, R., Wilschanski, M., Reiter, J., Shoseyov, D., Gileles-Hillel, A., Pugatsch, T., Davies, J. C., Short, C., Saunders, C., DeSouza, C., Sullivan, J. C., Doyle, J. R., Chandarana, K., & Kinnman, N. (2021). Ivacaftor in People with Cystic Fibrosis and a 3849+10kb C-->T or D1152H Residual Function Mutation.	Ann Am Thorac Soc, 18(3), 433-441.
Study 128 VX17-770-128	Clinical Study Report, November 2021: A Post Marketing Observational Study to Evaluate the Real-World Clinical Response to Ivacaftor Treatment in Patients with CF who Have Selected Ivacaftor Responsive CFTR Mutations	
IVA-responsive rare mutations population (non-clinical studies)		
P289	Nonclinical Study Report, June 2020: In vitro Pharmacological Profiling of CFTR Mutations in FRT Cells Using VX-445, TEZ, and IVA: Effects on Processing and Trafficking, and Chloride Transport	
Van Goor et al.	Van Goor, F., et al. (2014). "Effect of ivacaftor on CFTR forms with missense mutations associated with defects in protein processing or function."	J Cyst Fibros 13(1): 29-36.
Yu et al.	Yu, H., et al. (2012). "Ivacaftor potentiation of multiple CFTR channels with gating mutations."	J Cyst Fibros 11(3): 237-245.

Source: Table 2.2.1 p52-54 of the submission
CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane regulator; FRT = Fischer Rat Thyroid; IVA = ivacaftor; TEZ = Tezacaftor; US = United States.

6.6 The key features of the studies are summarised in Table 4. The majority of the studies were relatively short in the context of ongoing and chronic therapy in CF patients. Study 122 and Study 128 provide evidence regarding the longer-term benefit of therapy; however, cohort attrition and missing data was a potential source of bias in these studies. A sensitivity analysis was conducted in a subset of 69 patients from Study 128 who had non-missing $ppFEV_1$ data in the 3 years before and after ivacaftor initiation.

6.7 The submission claimed superior efficacy compared to BSC based on absolute change from baseline in: percent predicted forced expiratory volume in 1 minute ($ppFEV_1$), sweat chloride (SwCl), nutritional status (weight, length, weight-for-length z-scores, weight-for-length-for-age z-scores and weight-for-length percentiles), faecal-elastase-1 (FE-1), immunoreactive trypsinogen (IRT), and occurrences of pulmonary exacerbations (PEx). While a superiority claim was not made based on changes in either body mass index (BMI) or the CFQ-Respiratory Domain (CFQ-R), results for those endpoints were included given BMI is an indicator of nutritional status, and the CFQ-R is a validated and widely used patient-reported outcome for CF[3] that assesses overall health and well-being.

6.8 $ppFEV_1$ has previously been considered the primary endpoint upon which to assess the efficacy of ivacaftor (para 6.19, lumacaftor/ivacaftor PSD, July 2019 PBAC meeting, para 6.18, ivacaftor PSD, March 2018 PBAC meeting). Changes in SwCl were

[3] https://respiratory-research.biomedcentral.com/articles/10.1186/s12931-017-0592-z

considered to provide evidence of biological activity (para 6.22, ivacaftor PSD, March 2019 PBAC meeting).

6.9 The submission proposed 2 minimum clinical important difference (MCID) definitions for 2 different outcomes.

- SwCl: for changes in SwCl to be considered clinically important, the submission stated that levels must decrease toward the threshold used for CF diagnosis:
  - ≤30 mmol/L: CF is very unlikely
  - 30 to 59 mmol/L: CF is possible
  - ≥60 mmol/L: CF is likely to be diagnosed
- The National Health Service (NHS) of England considers a 30% reduction in SwCl, or SwCl falling below 60 mmol/L, as indicating a response to ivacaftor treatment.[4]
- FE-1: an increase in FE-1 level suggesting rescue of pancreatic function. The PBAC has previously seen these MCIDs for SwCl and pancreatic function (ivacaftor commentary, March 2019 PBAC meeting).

6.10 Across the studies, outcomes were reported at different time points (e.g. Study 113 reported absolute change from baseline in ppFEV$_1$ at 2 weeks whereas Study 128 reported the same outcome at 3 years), which limited comparability between studies. Comparative data relative to placebo (BSC) was presented for Study 108, Study 110, Study 113 and Study 127, however was not presented for Study 112 or Study 124 (single-arm studies) or for some outcomes in Study 113. Study 122 provided a within group comparison as well as comparative data with a historical cohort who had never been exposed to ivacaftor. Study 128 provided a within group comparison only.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Gating population					
Study 124	Part A Group 2: 6 to < 12 months (n=6) Group 3: 3 to < 6 months (n=6) Part B Group 6: 6 to < 12 months (n=11) Group 7: 0 to < 6 months (n=6)	OL, 24 weeks	High	Gating mutation aged 4 to < 12 months	Part A: pharmacokinetics, safety Part B: SwCl, FE-1, IRT, BMI, weight, height, hospitalisations, PEx
R117H population					

[4] NHS England, 2015, Clinical Commissioning Policy: Ivacaftor for Cystic Fibrosis (named mutations).

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Study 110	69	R, DB, MC 24 weeks	Low	R117H mutation aged ≥ 6 years	ppFEV$_1$, SwCl, BMI, CFQ-R respiratory domain score, PEx
Study 112	69	OL, MC 104 weeks	Low	R117H or non-G551D mutation aged ≥ 6 years	Safety, ppFEV$_1$, BMI, SwCl, CFQ-R respiratory domain, PEx
Study 122	369	3 years before and after ivacaftor treatment initiation	NA	R117H mutation aged ≥ 2 years	ppFEV$_1$, PEx, BMI, weight, height, death or transplant, hospitalisations, CF-complications, pulmonary microorganisms
Non-splice RF population					
Study 108	248	R, DB, MC	Low	CF patients aged ≥12 years who were heterozygous for the F508del-CFTR and an RF mutation	ppFEV$_1$, CFQ-R respiratory domain, SwCl, PEx, FEV$_1$, FVC, FEF25-75%, FEV$_1$/FVC, BMI, weight, height, QoL
Study 113	24	R, DB	Low	Patients aged ≥ 12 years with clinical or molecular evidence of RF mutation	ppFEV$_1$, LCI$_{2.5}$, SwCl, safety, BMI
Study 127	38	R, DB, SC	Low	3849 + 10KB C→ T or D1152H mutation aged ≥ 6 years	LCI$_{2.5}$, SwCl, ppFEV$_1$, CFQ-R respiratory domain
Study 128	349	3 years before and after ivacaftor treatment initiation	NA	IVA responsive residual function aged ≥ 2 years	ppFEV$_1$, PEx, hospitalisations; BMI, weight, CF related complications, pulmonary microorganisms
IVA-responsive rare mutations population (non-clinical studies)					
Yu et al.	NA	Non-clinical study	NA	NA	In vitro pharmacological response to ivacaftor
Van Goor et al.	NA	Non-clinical study	NA	NA	In vitro pharmacological response to ivacaftor
P289	NA	Non-clinical study	NA	NA	In vitro pharmacological response to ivacaftor

Sources: Study 124: Table 2.3.1 p62, Table 2.3.2, p63; Table 2.3.9 pp69-70; Study 126: p90; Study 110: Table 2.4.2 pp92-93, Table 2.4.8 p100; Study 112: p105, pp2-5 Attachment 8; Study 113: p128, Table 2.7.3 p132; Study 127: Table 2/7/10 p140; Study 128 pp2-3 Attachment 17; Study 108 Table 2.7.32 p177; of the submission.

BMI = body mass index; CFQ-R = Cystic Fibrosis Questionnaire - Revised; DB = double blind; FE-1 = faecal elastase-1; FVC = forced vital capacity; IRT = immunoreactive trypsinogen; IVA = ivacaftor; LCI2.5 = lung clearance index; MC = multi-centre; 2.5; NA = not applicable; OL = open label; PEx = pulmonary exacerbations; ppFEV1 = per cent predicted forced expiratory volume in one second; QoL = quality of life; R = randomised; RF = residual function; SC = single centre; SwCl = sweat chloride.

Comparative effectiveness

Gating population (Study 124)

6.11 Based on the results from Study 124, treatment with ivacaftor over 24 weeks in CF patients aged 4 to 12 months with a gating (Class III) mutation resulted in an improvement in the primary, secondary and other efficacy endpoints from baseline. The findings are summarised in Table 5.

6.12 With respect to absolute change from baseline, mean SwCl at Week 24 fell below the threshold for diagnosing CF, thereby meeting the MCID definition proposed by the submission. SwCl decreased by 57.4% in Group 6 (aged 6 to < 12 months) and 61.3% in Group 7 (aged 0 to < 6 months), thereby meeting the NHS definition of response to ivacaftor treatment. The PBAC noted the mean absolute change in SwCl from baseline for this population (-62 mmol/L to -72 mmol/L) was broadly similar to the outcomes observed in patients aged 12 to 24 months, 2 to 5 years and ≥ 6 years, which ranged from -47 mmol/L to -58 mmol/L (para 6.10, ivacaftor PSD, March 2019 PBAC meeting and Table 3, ivacaftor PSD, November 2016 PBAC meeting).

6.13 With respect to change in nutritional status, absolute change from baseline in nutritional parameters at Week 24 improved for weight and length, and remained relatively stable for weight-for-age-z score, length-for-age z score and weight-for-length-for-age z score. Weight-for-length z-score remained stable for Group 6 but increased for Group 7. It is not clear whether these improvements in nutritional parameters are due to the effect of ivacaftor treatment, or children's natural growth and progression.

6.14 With respect to absolute change from baseline to week 24, mean (SD) change for FE-1 was 159.3 µg/g (154.4 µg/g) for Group 6 and 181.0 µg/g (122.9 µg/g) for Group 7. This met the submission's proposed MCID (defined as any increase in FE-1) and were above the threshold of 200 µg/g established for pancreatic insufficiency[5].

[5] Singh & Schwarzenberg (2017). Pancreatic insufficiency in Cystic Fibrosis. Journal of Cystic Fibrosis. 16 (2), S70-S78.

Table 5: Summary of the key efficacy outcomes in Study 124 (FAS)

Outcome definition	N (Group 6, Group 7)	Descriptive summary	Group 6	Group 7
			Mean absolute change from baseline mean (SD)	
Sweat Chloride	11, 6	Mean SwCl at Week 24 for both groups fell below the threshold for diagnosing CF, thereby meeting the MCID definition proposed by the submission. SwCl fell by 57.4% in Group 6 and 61.3% in Group 7, thereby meeting the NHS definition.	-62.3 (-73.5, -31.0)	-72.3 (-97.5, -42.0)
FE-1 levels at Week 24 (µg/g)[a]	9, 4	FE-1 improved for both groups at Week 24, and were above the threshold of 200 ug/g established for pancreatic insufficiency.	159.3 (154.4)	181.0 (122.9)
Serum IRT levels at Week 24 (ng/L) [a]	7, 4	The serum IRT levels decreased over 24 weeks of ivacaftor treatment.	-406.2 (363.3)	-593.8 (402.5)
Weight at Week 24 (kg) [a]	11, 6	Weight gain was observed during the study.	1.8 (0.7)	2.5 (0.6)
Weight-for-age z score at Week 24[a]	11, 6	Mean weight-for-age z-score remained stable during the study	0.36 (0.54)	0.68 (1.12)
Length at Week 24[a]	11, 6	A small gain in length was observed during the study.	7.7 (3.5)	9.3 (2.1)
Length-for-age z-score at Week 24[a]	11, 6	Length-for-age z-score remained stable during the study.	0.27 (1.34)	0.56 (0.86)
Weight-for-length z-score at Week 24[a]	11, 6	Weight-for-length remained stable during the study for Group 6, and increased for Group 7.	2.8 (38.3)	20.0 (37.0)
Weight-for-length-for-age z-score at Week 24[a]	11, 6	Mean weight-for-length-for-age z-score remained stable during the study	0.26 (1.30)	0.68 (1.12)
Number of PEx through Week 24	11, 6	Definition 1[b] Group 6 There were 7 patients with a PEx with 10 total events. The observed event rate per year was 1.95. Group 7 There were 2 patients with a PEx with 2 total events. The observed event rate per year was 0.73.	NR	NR
		Definition 2[c] Group 6 There were 3 patients with a PEx with 4 total events. The observed event rate per year was 0.78. Group 7 There was 1 patient with a PEx with 1 event. The observed event rate per year was 0.37.	NR	NR

Source: Table 2.3.14 p75; Table 2.3.15 p70; Table 14.2.2.1.b6 pp173-196 Attachment 5; Table 14.2.2.1.b7 pp158-189 Attachment 6; Table 2.3.18 p82; Table 2.3.20 p78, Table 2.3.21 p78; of the submission.

CF = cystic fibrosis; FAS = Full Analysis Set; FE-1 = faecal elastase-1; IRT = immunoreactive trypsin; IVA = ivacaftor; MCID = minimum clinical important difference; NHS = National health Service; NR = not reported; PEx = pulmonary exacerbations; SD = standard deviation; SwCl = sweat chloride.

[a] Assessed as absolute change from baseline at Week 24.

[b] Definition 1: Treatment with oral, inhaled, or intravenous (IV) antibiotics AND fulfillment of one or more of the criteria from List A or List B, within 3 days before antibiotic start date through antibiotic stop date.

[c] Definition 2: Treatment with oral, inhaled, or IV antibiotics AND fulfillment of one criterion from List A or two criteria from List B, within the period 3 days before antibiotic start date through antibiotic stop date.

List A: Oxygen saturation < 90% on room air or ≥ 5% decrease from baseline; New lobar infiltrate(s) or atelectasis on chest x-ray; Haemoptysis (more than streaks on more than one occasion in past week).

List B: Increased work of breathing or respiratory rate (duration ≥ 3 days); New or increased adventitial sounds on lung examination (duration ≥ 3 days); Weight loss ≥ 5% decrease from highest value or decrease across one major percentile for age in past 6 months; Increased cough (duration ≥ 3 days); Worked harder to breathe during physical activity (duration ≥ 3 days); Increased chest congestion or change in sputum (duration ≥ 3 days).

R117H and non-splice RF population

6.15 A summary of the results for absolute change from baseline in $ppFEV_1$ is presented in Table 6. Results from all studies indicated an improvement in absolute change from baseline in $ppFEV_1$, where reported.

6.16 Study 110: an improvement in absolute change from baseline in $ppFEV_1$ (LS mean difference) of 2.11 (95% CI -1.13, 5.35; p=0.20) was observed for the ivacaftor arm compared to placebo.

6.17 Study 112: an improvement in absolute change from baseline in $ppFEV_1$ (LS mean (SE) change) of 3.0 (1.6) for the ivacaftor arm at 104 weeks.

6.18 Study 122: an improvement in absolute change from baseline in $ppFEV_1$ (mean (SD)) of 1.7 (9.7) in the 3 years following ivacaftor initiation. In contrast, in the supplementary historical cohort, mean $ppFEV_1$ tended to decrease numerically over the 3-year period. Data for the historical cohort should be interpreted with caution due to a different time frame for data collection (as compared with the ivacaftor arm in Study 122), changes in standard of care, and changes in registry data collection practices over time.

6.19 Subgroup analyses by age for Study 110, 112 and 122 showed mixed results in $ppFEV_1$ with regard to the comparison of ivacaftor and placebo arms. Notably, in Study 110, there was a statistically significant change in $ppFEV_1$ in favour of ivacaftor for those over 18 years of age (p=0.01), but in favour of placebo relative to ivacaftor in those 6 to 11 years of age (p=0.03). The Advisory Committee on Medicines (ACM) noted that this may be explained by the relatively good lung function (>90% $ppFEV_1$) at baseline in the younger age cohort in Study 110 and Study 112 (Ivacaftor, ACM meeting 308, February 2016). The natural disease progression for CF patients with R117H mutation, wherein lung function decline occurs later in life[6], may also explain this finding.

6.20 Study 127: an improvement in absolute change from baseline in $ppFEV_1$ (LS mean difference) of 2.7 (95% CI: 0.6, 4.7) for ivacaftor compared to placebo at 8 weeks.

R117H Gene Mutation. J Cyst Fibros. 2018 Jul; 17(4): 503–510.

There was a decline in $pFEV_1$ in the D1152H mutation subgroup of -0.1 (95% CI: -4.3, 4.1).

6.21 Study 128: an improvement in absolute change from baseline in mean $ppFEV_1$ of 1.7 (95% CI: 0.2, 3.2) and 2.2 (95% CI: 0.5, 3.9) in the sensitivity analysis.

6.22 The PBAC has previously considered an improvement of ≥ 10 percentage points in absolute change from baseline in $ppFEV_1$ to be the MCID (paragraph 6.10, ELX/TEZ/IVA PSD, November 2022 PBAC Meeting with March 2023 Addendum; paragraph 6.10, LUM/IVA PSD, March 2016 PBAC meeting; Section 12, ivacaftor, PSD, July 2013 PBAC meeting). None of the studies achieved a change in $ppFEV_1 \geq 10$ percentage points.

Table 6: Results of absolute change from baseline in $ppFEV_1$ across the trials

Trial, follow-up	n	Mean baseline (SD/SE)	Mean change (SD/SE)	n	Mean baseline (SD/SE)	Mean change (SD/SE)	Mean difference (95% CI)	P-value
	Ivacaftor			Placebo				
Study 108, average of w4 and w8	156	62.1 (14.6)	4.4 (0.5)	161	62.2 (14.3)	-0.3 (0.5)	**4.7 (3.7, 5.8)**	**<0.0001**
Study 110, w24	34	75.70[a]	2.57[b]	35	70.23	0.46[ab]	2.11 (-1.13, 5.35)	0.1979
Study 112, w104	65	71.8[a]	3.0[b]	NR	NR	NR	NR	NR
Study 113, w2	24	NR	NR	24	NR	NR	2.3[c] (95% CI: 0.4, 4.1)	NR
Study 122, w156	305	69.1 (24.8)	1.7 (9.7)	NR	NR	NR	NR	NR
Study 127, w8	38	74.0 (16.9)	0.2 (0.8)	38	74.0 (16.9)	-0.5 (0.8)	2.7 (0.6, 4.7)	NR
Study 128, w156	268	2.6[a]	1.7	NR	NR	NR	NR	NR

Source: Study 110: Table 2.4.8 p92, Table 11-1 p126 Attachment 7; Study 112: Table 11-3 p75 Attachment 8; Study 113: Table 2.7.3 p121; Study 127: Table 2.7.12 p132; Study 108: Table 2.7.37 p169 of the submission.
CI = confidence interval; NR = not reported; ppFEV1 = percent predicted forced expiratory volume in 1 second; SD = standard deviation; SE = standard error; w = week.
a SD/SE not reported
b LS mean
c posterior mean as calculated by Bayesian Hierarchical model
Bold indicates a statistically significant difference.

6.23 A summary of the results for absolute change from baseline in SwCl is presented in Table 7. A numeric reduction in SwCl was observed across all the studies that assessed this outcome. The SwCl MCID was met in all studies except Study 108.

6.24 A statistically significant reduction in SwCl was also observed in the subgroup analysis by age (6 to 11 years and ≥ 18 years subgroups) in Study 110 and in the ≥ 18 years subgroup in Study 112. In both studies SwCl fell below 60 mmol/L thereby meeting the MCID proposed by the submission.

6.25 For Study 113, the absolute change from baseline in SwCl (mean (SD) change) of −15.7 (14.8), met the MCID. No comparative data was available as this was measured at the end of the 8-week open-label period, after the 2-week crossover periods. For Study 127, there was an improvement in absolute change from baseline in SwCl (LS mean

difference) of -9.2 (95% CI: 12.4, -5.9) in the ivacaftor arm compared to placebo. Baseline SwCl was already below 60 mmol/L in Study 127.

Table 7: Results of absolute change from baseline in SwCl across the studies

Study, follow-up	n	Mean baseline (SD/SE)	Mean change (SD/SE)	n	Mean baseline (SD/SE)	Mean change (SD/SE)	Mean difference (95% CI)	P-value
	Ivacaftor			Placebo				
Study 110, w24	35	67.26[a]	-26.28[a, b]	35	73.44[a]	-2.31[a, b]	**-23.97[b] (-28.01, -19.93)**	**<0.0001**
Study 112, w104	59	60.9	-11.9[b]	NR			NR	NR
Study 113, w8	24	64.7 (25.7)	−15.7 (14.8)	NR	18	53.4	NR	NR
Study 127, w8	38	49.1 (24.0)	-9.3 (1.2) [b]	38	49.1 (24.0)	-0.1 (1.2) [b]	-9.2[b] (-12.4, -5.9)	NR
Study 108, average of w4 and w8	155	72.3 (25.7)	-4.9 (1.0) [b]	157	70.2 (25.7)	-0.4 (1.0) [b]	**-4.5 [b] (-6.7, -2.3)**	**<0.0001**

Source: Study 110: Table 2.4.8p92; Table 11-6 p132 Attachment 7; Study 112: Table 11-15 p91 Attachment 8; Study 113: Table 2.7.2 pp119-120; Supplementary Table 2 p6; Attachment 15; Study 127: Table 11-5 pp57-58 Attachment 16; Study 108: Table 2.7.40 p172; of the submission.

CI = confidence interval; NR = not reported; SD = standard deviation; SE = standard error; SwCl = sweat chloride; w = week.

a SD/SE not reported

b LS mean

Bold indicates a statistically significant difference.

6.26 A summary of the results for absolute change from baseline in BMI is presented in Table 8. There were numerical improvements for ivacaftor treated patients with respect to BMI.

Table 8: Results of absolute change from baseline in BMI across the trials

Trial, follow-up	n	Mean baseline (SD/SE)	Mean change (SD/SE)	n	Mean baseline (SD/SE)	Mean change (SD/SE)	Mean difference (95% CI)	P-value
	Ivacaftor			Placebo				
Study 110, w24	34	24.48[a]	0.49[ab]	35	23.07[a]	0.23[ab]	0.26[b] (-1.57, 2.09)	0.7780
Study 112, w104	65	23.75[a]	1.20[ab]	NR	NR	NR	NR	NR
Study 113, w8	NR	24.2 (4.8)	0.5 (0.7)	NR	NR	NR	NR	NR
Study 108, average of w4 and w8	156	NR	0.47 (0.80)[b]	161	NR	0.18 (0.81)[b]	NR	NR

Source: Study 110: Table 2.4.8p92; Table 11-9 p135 Attachment 7; Study 112: Table 11-8 p79 Attachment 8; Study 113: p3 Attachment 14; Study 108: Table 2.7.41 p172; of the submission.

BMI = body mass index; CI = confidence interval; NR = not reported; SD = standard deviation; SE = standard error; w = week.

[a] SD/SE not reported

[b] LS mean

6.27 In Study 108, the estimated PEx event rate per year was lower for the ivacaftor arm versus placebo (0.29 vs 0.63, p=0.0532). Study 110 calculated a hazard ratio for time to first PEx which was not statistically significant, (HR 0.928, p=0.8556). In Study 112, the annualised event rate for all PEx was 0.41. In Study 122, changes from pre-treatment baseline in the mean number of PEx events were lower in each of the 12-month intervals after ivacaftor treatment initiation. In Study 127 there were 2 PEx in 2 patients; 1 in the placebo group and 1 in ivacaftor. For Study 128, the percentage of patients who experienced ≥ 1 PEx, and the mean annualised number of PEx events

were numerically lower in each of the 3 study years after ivacaftor initiation than at baseline.

6.28 In Study 108, 22 (14.1%) subjects in the ivacaftor arm and 21 (13.0%) subjects in the placebo group had <200 μg/g of FE-1 (pancreatic insufficiency) at study baseline. The within group mean change in FE-1 from study baseline to the average of Week 4 and Week 8 was -16.1 μg/g the ivacaftor arm. In Study 110, a decrease from baseline at Week 24 in FE-1 was seen for the placebo group (15.2619 μg/g) while there was a slight increase for the ivacaftor group (0.1587 μg/g). However, the treatment difference of 15.4206 μg/g (95% CI: 29.4148, 60.2560) was not statistically significant (p = 0.4922). The investigators provided an interpretation that FE-1 was assessed as normal (> 200 μg/g) at Week 104 for all subjects in whom it was evaluated who rolled over from Study 110 into Study 112. One patient had low FE-1 (< 200 μg/g) at the end of the study period, i.e., below the threshold for pancreatic insufficiency.

6.29 For the outcome of absolute change from baseline in IRT, the within group mean change in IRT from study baseline to Week 8 was -23.2 ng/mL in the ivacaftor arm and -2.1 ng/mL in the placebo group.

6.30 A summary of the results for absolute change from baseline in the CFQ-R Respiratory Domain is presented in Table 9. Results for Study 108, 110, 112 and 127 show that patients in the ivacaftor arms experienced an improvement in the CFQ-R Respiratory Domain that met the prespecified MCID of 4 points.

Table 9: Results of absolute change from baseline in CFQ-R Respiratory Domain across the trials

Trial, follow-up	n	Mean baseline (SD/SE)	Mean change (SD/SE)	n	Mean baseline (SD/SE)	Mean change (SD/SE)	Mean difference (95% CI)	P-value
	Ivacaftor			Placebo				
Study 110, w24	33	75.27[a]	7.56[ab]	34	66.42[a]	-0.83[ab]	8.39[b] (2.17,14.61)	**0.0091**
Study 112, w104	65	68.6 (21.6)	8.3 (18.0)[b]	NR	NR	NR	NR	NR
Study 127, w8	38	62.3 (20.3)	17.1[b] (2.4)	38	62.3 (20.3)	-1.7[b] (2.3)	18.7 (12.5, 25.0)	NR
Study 108, average of w4 and w8	156	67.9 (16.9)	8.7 (1.0)	161	68.7 (18.3)	-1.0 (1.0)	9.7 (7.2, 12.2)	**<0.0001**

Source: Study 110: Table 2.4.8 p92, Table 11-12 p141; Study 112: Table 14.2.3.1 pp1229-1240 Attachment 8; Study 127: Table 11-6 p59 Attachment 16; Study 108: Table 2.7.39 p171; of the submission.
CFQ-R = Cystic Fibrosis Questionnaire-Revised; CI = confidence interval; NR = not reported; SD = standard deviation; SE = standard error; w = week.
a SD/SE not reported
b LS mean
Bold indicates a statistically significant difference.

IVA-responsive rare mutations population (nonclinical studies)

6.31 The submission presented 3 studies (Yu et al. (2012), Van Goor et al. (2014) and Report P289) to support the use of ivacaftor in approximately 92 rare mutations that are IVA-responsive based on FRT in vitro assays. The level of chloride transport for each mutant CFTR form was expressed as a percentage of normal CFTR. A response to ivacaftor was defined as > 10-percentage point increase over baseline in chloride transport. The submission claimed that > 10% net increase in chloride transport is

predictive or reasonably expected to predict clinical benefit. However, the submission also noted that with individual mutations, this magnitude of change in in vitro response is not correlated with the magnitude of clinical response. The TGA Delegate's Overview noted that the in vitro FRT assay data is not a predictor for clinical efficacy but identifies potentially responsive mutations (Ivacaftor, p12 TGA Delegate's Overview, November 2022). The ACM concluded that the clinical and FRT assay studies were sufficient to demonstrate efficacy of ivacaftor in the proposed indication. The ACM acknowledged that the statement on the predictive potential of the FRT assay in Section 5.1 of the PI is acceptable due to the supportive clinical data and biological relevance for gating mutations.

6.32 The mutations that were tested in the FRT assay, and their corresponding chloride transport response, were provided in the submission. The 92 mutations that achieved a positive in vitro response, and for which this submission is seeking a PBS listing, are included in the Ivacaftor PI.

6.33 There are a wide range of in vitro study techniques available to assess the sensitivity of mutations to drug or likely clinical efficacy; the Ussing technique described by the submission utilises FRT cell lines to assess sensitivity to drug (ivacaftor) in cell-lines which overexpress CFTR. The submission claimed that these in vitro assays could predict in vivo benefit, based on Ramalho et al. 2022. The evaluation noted this paper stated that positive in vitro findings require further evaluation for clinical efficacy.

6.34 The submission referenced 3 papers to support its in vitro to in vivo claim: van Goor et al. (2011), Veit et al. (2018) and Guerra at al. (2020). van Goor 2011 and Veit 2018 focussed on lumacaftor's efficacy in patients with a F508del mutation which is consistent with a valid mechanism of action.[7,8] The translation of in vitro to in vivo efficacy for patients with the F508del mutation does not necessarily mean that all mutations that demonstrate in vitro response will be predictive of clinical efficacy. Guerra et al. 2020 discussed a single case where in vitro efficacy predicted in vivo efficacy with the G970D mutation. The paper also discussed that whilst in vitro data may suggest efficacy, the dynamic genetic environment found in human cells can pose unique challenges. For example, in the G970R mutation (a class III gating mutation), messenger RNA decay caused a deletion of 59 amino acid residues, which caused little-to-no CFTR on the cell surface. This led to complete loss of function of potentiator/corrector therapy. The G970R mutation was included in Yu et al. (2012) study and demonstrated a > 40% change in chloride transport from baseline, but in Study 112 patients with a G970R mutation (n=3) did not demonstrate a positive ppFEV$_1$ response. Ivacaftor is not indicated for use in patients with this mutation[9].

[7] Van Goor, F., *et al.* (2011), Correction of the F508del-CFTR protein processing defect *in vitro* by the investigational drug VX-809, Proc Natl Acad Sci USA 108(46): 18843-18848.

[8] Veit, G., *et al.* (2018), Structure-guided combination therapy to potently improve the function of mutant CFTRs, Nat Med 24(11): 1732-1742.

[9] Kalydeko (ivacaftor), Clinical trials for patients age 6 years or older, https://www.kalydecohcp.com/trials-2-4-5

Both the G970D and G970R mutations appeared responsive to ivacaftor in animal-cell in vitro studies, and it was not until they were tested in human cells that the inefficacy of ivacaftor therapy was realised in patients with the G970R mutation.

6.35 Testing efficacy on animal cells in vitro is one of many steps that novel pharmacological treatments traditionally move through to identify potential treatment populations for clinical trials to demonstrate efficacy, and eventually reach clinical use. The FRT in vitro assays allow for high-throughput testing, however recent literature[10,11,12,13,14] has emphasised the importance of validating the results from animal cell in vitro assays with primary (human) cell in vitro assays. The approach adopted by the submission omits human cell in vitro testing and clinical trial efficacy data, relying on animal cell in vitro efficacy alone to predict clinical efficacy.

Comparative harms

6.36 In the gating mutation population, the adverse events (AEs) reported in Study 124 were consistent with the known safety profile of ivacaftor. These are summarised in Table 10.

[10] Pedemonte et al. (2010), Influence of cell background on pharmacological rescue of mutant CFTR, *Am J Physiol Cell Physiol 298: C866–C874.*

[11] Haggie et al. (2017), Correctors and Potentiators Rescue Function of the Truncated W1282X-Cystic Fibrosis Transmembrane Regulator (CFTR) Translation Product, The Journal of Biological Chemistry, 292(3), pp. 771–785.

[12] Cholon & Gentzsch (2018), Recent progress in translational cystic fibrosis research using precision medicine strategies, *Journal of Cystic Fibrosis 17 (2018) S52–S60.*

[13] Berkers et al. (2019), Rectal Organoids Enable Personalized Treatment of Cystic Fibrosis, *Cell Reports 26, 1701–1708.*

[14] Dekkers et al. (2016), Characterizing responses to CFTR-modulating drugs using rectal organoids derived from subjects with cystic fibrosis, *Sci. Trans. Med. 8(344).*

Table 10: Summary of the key adverse events in Study 124

	Part A		Part B	
System organ class[a] Preferred Term	**Group 2 IVA 25/50 mg N = 6, n (%)**	**Group 3 IVA 25/50 mg N = 6, n(%)**	**Group 6 IVA 50mg N = 11, n (%)**	**Group 7 IVA 25mg N = 6, n (%)**
Patients with any AEs	4 (66.7)	3 (50.0)	10 (90.9)	6 (100.0)
Patients with related AEs	3 (50)	0	2 (18.2)	0
Patients with AEs leading to treatment discontinuation	0	0	0	0
Patients with AEs leading to treatment interruption	0	0	1 (9.1)	0
Patients with SAEs	0	0	3 (27.3)	1 (16.7)
Patients with AEs leading to death	0	0		0
Patients with any AEs	4 (66.7)	3 (50.0)	10 (90.0)	6 (100.0)
Mild	3 (50)	1 (16.7)	4 (36.4)	4 (66.7)
Moderate	0	1 (16.7)	4 (36.4)	1 (16.7)
Severe	1 (16.7)	1 (16.7)	2 (18.2)	1 (16.7)
Life-threatening	0	0	0	0
Missing	0	0	0	0

Source: Table 2.3.24 p87; Table 2.3.25 p88; Table 2.3.26 p89; of the submission; pp93-94; Table 14.3.1.5.a2 p259; Table 14.3.1.1.b6 pp271-278; Table 12-3 p96; Table 14.3.1.2.b7 pp257-264; Attachment 5 of the submission

AE = adverse event; IVA = ivacaftor; SAE = serious adverse event.

[a] subject with multiple events within a category (Any, SOC, or PT) was counted only once in that category

6.37 The AEs reported in Study 108, Study 110, Study 112, Study 113 and Study 127 were consistent with the known safety profile of ivacaftor. There was no difference in measurable safety outcomes between the ivacaftor and placebo arms, and high-grade AEs and treatment interruption/discontinuations were rare and balanced between arms. A summary of the AEs for Study 108 is presented in Table 11. A summary of the AEs for the remaining studies is not presented due to the small sample size in each study.

Table 11: Summary of AEs in Study 108 and Study 110, Safety Set.

	Study 108				Study 110			
	Placebo N=162 n (%)	**IVA N=157 n (%)**	**RR (95% CI)[a]**	**RD (95% CI)[a]**	**Placebo N=162 n (%)**	**IVA N=157 n (%)**	**RR (95% CI)[a]**	**RD (95% CI)[a]**
Patients with any AEs	126 (77.8)	114 (72.6)	0.93 (0.82,1.06)	-0.05 (-0.15,0.04)	35 (100.0)	32 (94.1)	0.94 (0.87,1.03)	-0.06 (-0.06,0.02)
Patients with related AEs	38 (23.5)	31 (19.7)	0	-0.04 (-0.13,0.05)	7 (20.0)	3 (8.8)	0.44 (0.12,1.57)	-0.11 (-0.27,0.05)
Related	5 (3.1)	2 (1.3)	0	-0.02 (-0.05,0.01)				
Patients with AEs by maximum severity								
Mild	63 (38.9)	55 (35.0)	0.90 (0.682,1.20)	-0.04 (-0.14,0.07)	10 (28.6)	17 (50.0)	1.75 (0.94,3.26)	0.21 (-0.04,0.44)
Moderate	54 (33.3)	51 (32.5)	0.97 (0.71,1.33)	-0.01 (-0.11,0.01)	20 (57.1)	14 (41.2)	0.72 (0.44,1.18)	-0.16 (-0.38,0.07)
Severe	8 (4.9)	8 (5.1)	1.03 (0.40,2.68)	0.00 (-0.05,0.05)	5 (14.3)	1 (2.9)	0.21 (0.03,1.67)	-0.11 (-0.24,0.02)
Life-threatening	1 (0.6)	0	0	-0.01 (-0.02,0.01)	0	0	0	0
Patients with SAEs	14 (8.6)	10 (6.4)	0.74 (0.34,1.61)	-0.02 (-0.08,0.04)	6 (17.1)	4 (11.8)	0.69 (0.219,2.22)	-0.05 (-0.22,0.11)
Patients with related SAEs	2 (1.2)	2 (1.3)	1.03 (0.15,7.24)	0 (-0.02,0.03)	0	0	0	0 (0,0)
Patients with AEs leading to treatment interruption	6 (3.7)[a]	5 (3.2)	0.86 (0.273,2.76)	-0.01 (-0.05,0.04)	2 (5.7)	1 (2.9)	0.51 (0.05,5.42)	-0.03 (-0.12,0.07)
Patients with AEs leading to death	0	0	0	0	0	0		0

Source: Table 2.7.44 p191; Table 2.7.45 p192 of the submission

AE = adverse event; CF = cystic fibrosis; CI = confidence interval; CPK = creatine phosphokinase; IVA = ivacaftor; PEx = pulmonary exacerbations; RD = risk difference; RR = relative risk; SAE = serious adverse event

[a] This analysis was not powered to detect statistical differences in the occurrence of safety events; apparent differences shown in relative measures of effect are exploratory only.

Benefits/harms

6.38 Study 124 was a non-comparative study. As such, it was not possible to present an assessment of benefits-to-harms for ivacaftor compared with BSC in the gating mutation population aged 4 to < 12 months of age.

6.39 A summary of the comparative benefits and harms for ivacaftor versus BSC is presented in Table 12. On the basis of direct evidence from Study 108 presented in the submission, patients with a non-splice RF mutation aged ≥ 12 years treated with ivacaftor achieved 4.7 percentage point increase in lung capacity (as measured by $ppFEV_1$) compared with placebo over a 4 to 8 week follow up. On the basis of direct evidence from Study 110 presented in the submission, patients with an R117H mutation aged ≥ 6 years treated with ivacaftor achieved 2 percentage points increase in the lung capacity (as measured by $ppFEV_1$) compared with placebo over a 4 to 8 week follow up.

6.40 On the basis of direct evidence from Study 108 and Study 110, presented in the submission, patients treated with ivacaftor have no increase in the overall likelihood of harms compared with BSC.

Table 12: Summary of comparative benefits and harms for ivacaftor versus placebo

Benefits: Change from baseline in absolute change in $ppFEV_1$							
Trial	**Ivacaftor**			**PBO**			**Mean difference (95% CI)**
	N	**Mean change**	**SE**	**N**	**Mean change**	**SE**	
Study 108	156/157	4.4	0.5	153/168	-0.3	0.5	4.7 (3.7, 5.8)
Study 110	32/34	2.57	NR	32/35	0.46	NR	2.11 (-1.13, 5.35)

Harms						
	Ivacaftor N=34	**PBO N=35**	**RR (95% CI)**	**Event rate/100 patients**		**RD (95% CI)**
				ivacaftor	**placebo**	
Patients with any AE						
Study 108	114 (72.6)	126 (77.8)	0.93 (0.82,1.06)	73	78	-0.05 (-0.15,0.04)
Related AE						
Study 108	31 (19.7)	38 (23.5)	0.84 (0.55, 1.28)	20	24	-0.04 (-0.13,0.05)
	Ivacaftor N=157	**PBO N=168**	**RR (95% CI)**	**Event rate/100 patients**		**RD (95% CI)**
				ivacaftor	**placebo**	
Patients with any AE						
Study 110	32 (94.1)	35 (100.0)	0.94 (0.87,1.03)	94	100	-0.06 (-0.06,0.02)
Related AE						
Study 110	3 (8.8)	7 (20.0)	0.44 (0.12,1.57)	9	20	-0.11 (-0.27,0.05)

Source: Study 108: Table 2.7.36 p168; Table 2.7.44 p175; Study 110: Table 2.4.8 p92; Table 2.4.11 p94; of the submission.
AE = adverse event; CI = confidence interval; N = number of patients; NR = not reported; PBO = placebo; ppFEV1 = percent predicted forced expiratory volume in 1 second; RD = risk difference; RR = relative risk; SE = standard error.

Clinical claim

Gating population

6.41 The submission made a clinical claim that ivacaftor plus BSC is superior in terms of efficacy and comparable in terms of safety relative to BSC alone in patients aged 4 months or older with a gating (Class III) mutation. Study 124 was a single arm study and therefore it did not provide comparative evidence against BSC. The submission did not compare the incremental benefit of commencing ivacaftor at 4 months with commencement of CFTR modulator(s) at a later age. Overall, the benefits of treatment with ivacaftor demonstrated by Study 124 should be interpreted with caution due to the small size of the study (n=17), short duration of follow up and the absence of a control group.

6.42 The submission claimed the reduction in SwCl seen in Study 124 was indicative of treatment effect, and was similar to that seen in the 2 to 5 year old population. The prognostic impact of the improvement in SwCl in terms of patient survival and quality of life was not addressed.

6.43 The PBAC has previously considered a reduction in SwCl as evidence of biological activity (paragraph 6.22, ivacaftor PSD, March 2019 PBAC meeting) for CFTR modulators in the treatment of patients with CF. In the absence of ppFEV$_1$ results, the PBAC has previously considered the comparative improvements in SwCl in the 1 to 2 years cohort, in relation to older age cohorts, as an uncertain but plausible measure of effectiveness (paragraph 6.22, ivacaftor, PSD, March 2019 PBAC meeting).The evaluation considered it would appear reasonable that the same interpretation of the clinical claim applied to older cohorts in the gating mutation population is applicable to the consideration of the evidence provided in this submission and applied to the use of ivacaftor in the 4 to <12 months age group for the gating population. The ESC considered the clinical benefit of starting ivacaftor at 4 months of age compared to starting ivacaftor at 1 year of age and transitioning to ELX/TEZ/IVA at 6 years of age (for some patients with a gating mutation) remained uncertain.

R117H or non-splice RF population

6.44 Overall, the claim presented by the submission of superior efficacy of ivacaftor compared to BSC in the R117H and non-splice RF population was not well supported by the evidence due to the requested age group not being aligned with the trial population's age groups, small study sample sizes (Study 110, Study 112, Study 113, Study 127), short duration of follow up (Study 110, Study 113, Study 127, Study 108), lack of comparator for all or some outcomes (Study 112 and Study 113), cohort attrition and missing data (Study 128), and lack of statistical significance in the reporting of several outcomes.

6.45 Study 113, Study 127 and Study 108 included patients with a splice mutation which is not part of the TGA regulatory approval. Out of the 92 mutations for which this submission is seeking a listing, Study 113 included only 5 mutations, Study 127 included 1, Study 128 included 19. For Study 108, 96 (59.6%) patients had a Class V

non-canonical splice RF mutation at Period 1, and 65 (40.4%) had a Class II to IV RF mutation. The submission did not report how many of these are represented in the 92 mutations for which it sought listing. Thus, it is not possible to discern the applicability of the results from Study 108 to practice in Australia with respect to mutation status. Overall clinical evidence of in vitro responsive mutations was presented for 25% of the mutations for which this submission is seeking a PBS listing.

6.46 Given the aetiology of CF, difficulties in obtaining comparative data in infants with CF, and the results presented for intermediate outcomes (including reduction in SwCl), the evaluation considered it would appear reasonable that the same extrapolation of the clinical and safety claim applied to older cohorts in the R117H mutation population be applicable to the consideration of the evidence provided in this submission and applied to the use of ivacaftor in the ≥ 4 to months age group.

6.47 The ESC considered the clinical benefit of starting ivacaftor at 4 months of age compared to starting ELX/TEZ/IVA at 6 years of age (for the F/R117H population) or TEZ/IVA at 12 years of age (for the non-F/ RF) remained uncertain.

IVA-responsive rare mutations population (non-clinical studies)

6.48 The submission requested ivacaftor be listed for patients who have at least one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data, listing 92 eligible mutations. The submission did not provide robust evidence to support its claim that animal-cell in vitro efficacy would be predictive of clinical benefit in patients across all the mutations for which it sought a PBS listing. The tenuous relationship between FRT in vitro and in vivo efficacy means that there is a risk that ivacaftor may have reduced or absent clinical effectiveness in at least some of the CFTR non-gating mutations requested for PBS listing. The evaluation considered the risk that listing ivacaftor for use in non-gating mutations may have reduced or absent clinical effectiveness would be borne by Australian CF patients and the Australian Government, and is compounded by the submission's anticipation of lifetime treatment for eligible patients, with no proposed treatment stopping rules in non-responding patients. The ESC acknowledged the challenges of conducting clinical studies in these patients (as noted in the PSCR); however, the uncertainty regarding the benefit of treating this population with ivacaftor remained.

6.49 The ESC noted there was limited (and for some populations, no) clinical data provided in the submission to support the clinical claim that ivacaftor is superior in terms of effectiveness and non-inferior in terms of safety compared to BSC alone. The pre-PBAC response acknowledged the limitations of the data presented in the submission due to the constraints of conducting clinical trials in young patients and in those with rare CFTR mutations. The pre-PBAC response stated a comprehensive literature search had been conducted to identify all relevant sources such as clinical trials, real-world studies and non-clinical studies.

6.50 The PBAC considered that the claim of superior comparative effectiveness (for all populations) was uncertain but, overall, was likely to be reasonable.

Safety

6.51 The submission described ivacaftor as comparable in terms of safety compared to BSC. The evidence provided by the submission suggested that ivacaftor appeared to be generally well tolerated with a comparable side-effect profile with the placebo throughout the trial periods. No critical safety concerns regarding the safety profile for the proposed registered indication were raised.

6.52 The PBAC considered that the claim of comparable safety was reasonable.

Economic analysis

6.53 The submission did not present an economic evaluation, which was justified on the basis of inherent limitations in the currently available data to inform a cost-effectiveness analysis (CEA) of ivacaftor in the requested populations which the sponsor stated are unlikely to be resolved in the future. For the gating population, the young age of participants was cited as a limiting factor in measuring relevant outcomes previously used in CEAs for ivacaftor, such as lung function (i.e., ppFEV$_1$) through spirometry. For the additional populations, the genotype rarity of the RF and IVA-responsive rare mutations was cited as a limitation, making it impossible to run appropriately powered RCTs. For the R117H population, the submission argued that these patients can access ELX/TEZ/IVA from 6 years of age if they carry an F508del (F) mutation on the other allele but those without an F mutation have no access to CFTR modulator treatment. However, the sponsor argued that these limitations should not preclude access to CFTR modulators (making an age-based, rarity- and clinical need equity argument) and pragmatically requested that ivacaftor be made available for these additional patients at the same price as it is currently reimbursed through the PBS.

6.54 The age-based equity argument was consistent with that in a previous submission to the PBAC to extend the listing of ivacaftor for treatment of CF in patients with a G551D or other class III gating mutations aged 12 to 24 months of age, which also did not present an economic evaluation (paragraph 6.24, ivacaftor PSD, March 2019 PBAC meeting). The PBAC considered that the cost-effectiveness of the additional year of treatment with ivacaftor, compared with BSC, was unknown; however, the ESC stated that the incremental cost per QALY gained of the additional year of treatment was likely to be high (paragraph 6.25, ivacaftor PSD, March 2019 PBAC meeting).

6.55 A previous PBAC submission to expand the listing of ELX/TEZ/IVA for CF patients aged 6-11 years with an F508del (F) mutation in the CFTR gene also did not present an economic evaluation for those with an RF or R117H mutation on the other allele (F/RF and F/R117H), due to a lack of clinical evidence in these patient cohorts (paragraph 6.41, ELX/TEZ/IVA PSD, November 2022 PBAC meeting with March 2023 addendum). The PBAC recommended listing of ELX/TEZ/IVA, noting the treatment was expected to address a high and urgent unmet clinical need for these patient populations as they currently have no alternative treatment options (until they are at least 12 years of age)

(paragraph 7.14, ELX/TEZ/IVA PSD, November 2022 PBAC meeting with March 2023 addendum).

6.56 The ESC considered it was unlikely ivacaftor would be cost effective at the requested price. Given the uncertainties associated with the clinical benefit and therefore the cost-effectiveness, the ESC considered it may not be reasonable to pay more than the lowest cost CFTR modulator for this additional population. The pre-PBAC response stated that to consider ivacaftor and ELX/TEZ/IVA comparable to the less effective therapy, TEZ/IVA, is not appropriate and is not a proposition the sponsor can accept.

Ivacaftor cost/patient/year

Table 13: Drug cost per patient for ivacaftor

	Trials included in submission			Financial estimates		
Cost per 28-day pack (effective)[a]	$ [redacted]			$ [redacted]		
Compliance	**Gating population**	**Additional populations**		**Gating population**	**Additional populations**	
	Study 124: 99.9% and 99.3% in both groups	F/(R117H or RF); Non-F/RF; F/rare (Study 108, 110 and 112)	100%	100%	F/(R117H or RF); Non-F/RF; F/rare	95%
		Non-F/R117H; Non-F/rare (Study 108, 110 and 112)	100%		Non-F/R117H; Non-F/rare	85%
Number of scripts per year	**Gating population**	**Additional populations**		**Gating population**	**Additional populations**	
	8.66 [b]	F/(R117H or RF); Non-F/RF; F/rare	13.04	8.69 [b]	F/(R117H or RF); Non-F/RF; F/rare	12.39
		Non-F/R117H; Non-F/rare	13.04		Non-F/R117H; Non-F/rare	11.09
Cost/patient/year (using effective price) [c]	**Gating population**	**Additional populations**		**Gating population**	**Additional populations**	
	$ [redacted]	F/(R117H or RF); Non-F/RF; F/rare	$ [redacted]	$ [redacted]	F/(R117H or RF); Non-F/RF; F/rare	$ [redacted]
		Non-F/R117H; Non-F/rare	$ [redacted]		Non-F/R117H; Non-F/rare	$ [redacted]

Source: Table constructed during the evaluation, using inputs provided by the submission.

[a] Cost per pack is the same regardless of dose or formulation

[b] Scripts per year multiplied by (8/12) that represents additional 8 months of treatment with extension to current PBS listing of ivacaftor for this patient population

[c] Calculation conducted during the evaluation, (cost per packet * compliance * number of scripts per year) using inputs provided by submission

6.57 Drug costs per patient per year are presented in Table 13. While treatment is ongoing for the lifetime of the patient, costs for the gating population are restricted to those associated with the additional eight months of therapy that would be permitted for a new patient commencing therapy under the proposed listing (i.e., from the proposed 4 months of age, up to 12 months of age at which time a patient can already access ivacaftor on the PBS).

6.58 The estimated drug cost per patient per year for ivacaftor ($ [redacted] to $ [redacted] depending on population) is greater than the cost per patient per year for ELX/TEZ/IVA ($ [redacted] in CF patients over 12 years of age, $ [redacted] in CF patients 6 to 11 years of age) (Table 8, ELX/TEZ/IVA PSD, Dec 2021 PBAC meeting and Table 18, ELX/TEZ/IVA PSD, March 2023 PBAC meeting) and TEZ/IVA ($ [redacted]). As noted earlier, patients with an F508del mutation (F) are expected to switch to ELX/TEZ/IVA from ivacaftor from 6 years of age and patients with a non-splice RF mutation are expected to switch to TEZ/IVA from 12 years of age. No evidence was presented demonstrating a larger benefit with ivacaftor in younger patients to support a higher price being cost-effective.

6.59 The pre-PBAC response stated the effective pack price applied in the financial estimates of $ [redacted] was calculated using the assumptions applied in calculating the IVA offsets for the listing of ELX/TEZ/IVA i.e., based on an ivacaftor cost per patient of $ [redacted] (paragraph 6.55, ELX/TEZ/IVA PSD, July 2021 PBAC meeting) divided by 10.51 scripts (assuming 80% compliance).

Estimated PBS usage & financial implications

6.60 This submission was not considered by the Drug Utilisation Sub-Committee (DUSC). The submission used a prevalence based epidemiological approach, with the utilisation and budget impact estimates calculated separately for each of the specified patient populations. The eligible patient populations were converted to full-time equivalent (FTE) patients. Key inputs for financial estimates are presented in Table 14.

Table 14: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Gating population aged 4 months to 12 months		
Prevalent population	6 – based on the average of the eligible population from ACDFR reports between 2013 and 2021.	The annual growth rate of the total population was applied to the prevalent population for forward estimates; however, this made only a negligible impact to the prevalent population.
Uptake rate	50%. Based on local clinical opinion, uptake is expected to be modest due to the relatively narrow age bracket, however many parents will elect for treatment in their child as soon as they are eligible.	This could not be verified as the submission did not present the sources of this statement.
Discontinuation rate	0%. Based on clinical trial data (Study 124) and 2021 ACDRF report which showed that no patients aged between 1 and 5 years of age have discontinued ivacaftor in Australia.	This aligns with the PBAC submission for ivacaftor for CF patients aged 12–24 months old with a gating mutation (ivacaftor submission, March 2019 PBAC meeting), however is optimistic and may risk overestimating drug utilisation and financial estimates
Compliance rate	100%. Based on clinical opinion that it has been consistently observed that compliance is higher in younger populations due to parental supervision.	This rate is optimistic and may risk overestimating drug utilisation and financial estimates
MBS items	Liver Functions tests (LFTs): MBS item 66512- calculated using default 80% rebate rate	It is recommended in the PI for ivacaftor that LFTs be collected prior to commencement of therapy, every three months for the first year, and annually thereafter. The PI also recommends two

Parameter	Value applied and source	Comment
		ophthalmological visits (MBS item 104); one at baseline and one after treatment initiation. The submission claimed that considering these patients would receive LFTs and ophthalmological visits required for ivacaftor initiation in the absence of the requested listing, they are already captured and thus are not considered in this analysis- only an additional LFT related to the additional 8 months of ivacaftor treatment was included.
Additional populations aged 4 months and older		
Prevalent population	83 – based on bespoke data request from ACFDR for the year 2021	The pre-PBAC response updated this to 90 based on 2022 data from the ACFDR.
Uptake rate	F/(R117H or RF); non-F/R117H; non-F/RF: 80% F/IVA-responsive in vitro; non-F/IVA-responsive in vitro: 95% Uptake of ivacaftor was based on experience with existing listings of CFTR modulators and in consultation with Australian clinicians.	This could not be verified as the submission did not present the sources of this statement.
Discontinuation rates	F/(R117H or RF); non-F/RF; F/IVA-responsive in vitro: Year 1 1.4%, Year 2 4.2% non-F/R117H; non-F/IVA-responsive in vitro: Year 1 2.6%, Year 2 7.3% The submission used discontinuation rates applied in previous PBAC submissions for ELX/TEZ/IVA noting the similar efficacy and safety profile compared to ivacaftor.	This assumes that there is no discontinuation beyond year 2 of treatment which may risk overestimating drug utilisation and financial estimates (since treatment with ivacaftor is ongoing).
Compliance rate	F/(R117H or RF); non-F/RF; F/IVA-responsive in vitro: 95% non-F/R117H; non-F/IVA-responsive in vitro: 85% Compliance rates for the IVA-responsive populations were selected to align with previous CFTR modulator PBAC submissions and the well-established principle that compliance is higher in younger age groups where treatment is managed by parents.	The PBAC has previously considered that a compliance rate of 95% used in financial estimates for ELX/TEZ/IVA in CF patients aged 6-11 years old was higher than the 90% accepted for the same population aged ≥12 years and that this contributed to the total cost to the PBS likely being overestimated (paragraphs 6.70 and 6.72, ELX/TEZ/IVA PSD March 2023 Addendum).
MBS items	LFTs (MBS item 66512) Opthamology visits (MBS item 104) MBS expenditure was calculated using the default 80% rebate rate.	It is recommended in the PI for ivacaftor that LFTs be collected prior to commencement of therapy, every three months for the first year, and annually thereafter. The PI also recommends two ophthalmological visits: one at baseline and one after treatment initiation.

Source: Table 4.1.1, pp202-203 & Table 4.1.2, pp204-205 & Tables 4.2.2 and 4.2.3, p208 & Table 4.2.4, p209 & Table 4.2.6, p210 & Table 4.2.7, p211 & Table 4.3.4 p213 & Tables 4.8.1 and 4.8.2, p223 of the submission.

ACFDR = Australian Cystic Fibrosis Data Registry; CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; IVA = ivacaftor; LFT = liver function test; MBS = Medicare Benefits Schedule; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PI = Product Information.

6.61 A summary of the estimated use and financial implications is provided in Table 15.

Table 15: Estimated use and financial implications (effective price)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Gating (class III) patients aged 4 months to 12 months old						
Estimated extent of use						
Number of patients treated (FTE) [a]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed [b]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated financial implications of ivacaftor						
Cost to PBS/RPBS less co-payments (% net cost to PBS/RPBS)	$ [redacted][2] (3%)	$ [redacted][2] (3%)	$ [redacted][2] (3%)	$ [redacted][2] (3%)	$ [redacted][2] (3%)	$ [redacted][2] (3%)
F/(R117H or RF) patients aged 4 months and older						
Estimated extent of use						
Number of patients treated (FTE) [c]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed [d]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated financial implications of ivacaftor						
Cost to PBS/RPBS less co-payments (% net cost to PBS/RPBS)	$ [redacted][2] (44%)	$ [redacted][2] (44%)	$ [redacted][2] (44%)	$ [redacted][2] (44%)	$ [redacted][2] (44%)	$ [redacted][2] (44%)
Non-F/R117H patients aged 4 months and older						
Estimated extent of use						
Number of patients treated (FTE) [c]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed [e]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated financial implications of ivacaftor						
Cost to PBS/RPBS less co-payments (% net cost to PBS/RPBS)	$ [redacted][2] (33%)	$ [redacted][2] (33%)	$ [redacted][2] (33%)	$ [redacted][2] (33%)	$ [redacted][2] (33%)	$ [redacted][2] (33%)
Non-F/RF patients aged 4 months and older						
Estimated extent of use						
Number of patients treated (FTE) [c]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed [d]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated financial implications of ivacaftor						
Cost to PBS/RPBS less co-payments (% net cost to PBS/RPBS)	$ [redacted][2] (7%)	$ [redacted][2] (7%)	$ [redacted][2] (7%)	$ [redacted][2] (7%)	$ [redacted][2] (7%)	$ [redacted][2] (7%)
F/IVA-responsive rare mutations aged 4 months and older						
Estimated extent of use						
Number of patients treated (FTE) [c]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed [d]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated financial implications of ivacaftor						
Cost to PBS/RPBS less co-payments (% net cost to PBS/RPBS)	$ [redacted][2] (4%)	$ [redacted][2] (4%)	$ [redacted][2] (4%)	$ [redacted][2] (4%)	$ [redacted][2] (4%)	$ [redacted][2] (4%)
Non-F/IVA-responsive rare mutations aged 4 months and older						
Estimated extent of use						
Number of patients treated (FTE) [c]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed [e]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated financial implications of ivacaftor						
Cost to PBS/RPBS less co-payments (% net cost to PBS/RPBS)	$ [redacted][2] (9%)	$ [redacted][2] (9%)	$ [redacted][2] (9%)	$ [redacted][2] (9%)	$ [redacted][2] (9%)	$ [redacted][2] (9%)
Net financial implications						
Net cost to PBS/RPBS	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Net cost to MBS [f]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Net cost to Government	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]

Source: Table 4.3.1, p215 of the submission, Table 4.3.3, p216 of the submission, Table 4.3.5, p214 of the submission, Table 4.6.1 and 4.6.2, p224 of the submission, Table 4.7.1 and 4.7.3, p225 of the submission, Excel workbook "Vertex Ivacaftor (Kalydeco) 4m responsive UCM-Release-3-Workbook-v108 Jul2023" sheet 3c Impact – proposed (eff).

FTE = Full time equivalent; IVA = ivacaftor; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme

[a] Calculated (6 * 0.5 * (8/12))

[b] Assuming 13.04 scripts per year (100% compliance rate), fluctuations in script numbers due to rounding of FTE patients

[c] incident patients are assumed to initiate treatment on average halfway through a year, patients discontinuing treatment on average are expected to discontinue halfway through a year (50% first year-on, year off adjustments)

[d] Assuming 12.39 scripts per year (95% compliance rate), fluctuations in script numbers due to rounding of FTE patients

[e] Assuming 11.09 scripts per year (85% compliance rate), fluctuations in script numbers due to rounding of FTE patients

[f] MBS expenditure was calculated using the default 80% rebate rate

The redacted values correspond to the following ranges:

[1] < 500

[2] $0 to < $10 million

[3] $10 million to < $20 million

6.62 The total cost to the PBS/RPBS of listing ivacaftor was estimated to be $10 million to < $20 million in Year 6, and a total of $90 million to < $100 million in the first 6 years of listing. It is estimated that 3% of the incremental cost is attributable to the gating population; 44% is attributable to F/(R117H or RF) patients; 33% is attributable to Non-F/R117H patients; 7% to Non-F/RF patients; 4% to F/IVA-responsive rare mutation patients; and 9% to Non-F/IVA-responsive rare mutation patients.

Quality Use of Medicines

6.63 The submission did not present a discussion of quality use of medicines issues. However, the PBAC has previously considered that administration of ivacaftor granules mixed with food presents a wastage risk in very young children (potentially through regurgitation of the drug mixed with food, or refusal to eat, and drug stability of only one hour when mixed), which the ESC considered may have a considerable impact on cost-effectiveness of ivacaftor in clinical practice (paragraph 6.32, ivacaftor PSD, March 2019 PBAC meeting).

Financial Management – Risk Sharing Arrangements

6.64 The submission stated that the proposed listing will necessitate an increase to the current cap levels set out in the Deed of Agreement for PBS listed ivacaftor indications, which is due to expire in November 2023. In addition, the proposed listing will increase the overlap between the patient populations included within the existing ivacaftor Deed and those included within the combined deed for LUM/IVA, TEZ/IVA and ELX/TEZ/IVA. As such, the sponsor proposed that ivacaftor be factored into the combined Deed such that it covers the entire CFTR modulator market. To assist in

facilitating this change, the sponsor is willing to move to a Special Pricing Arrangement for ivacaftor with an effective EMP of $ |.

6.65 The sponsor requested that the net cost shown in Table 15 be added to the sum of the two RSA expenditure caps for ivacaftor and LUM/IVA, TEZ/IVA and ELX/TEZ/IVA currently in place.

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

7 PBAC Outcome

7.1 The PBAC recommended that the listing for ivacaftor granules and tablets be extended to include the treatment of cystic fibrosis (CF) in patients aged 4 months and older who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) that is responsive to ivacaftor based on clinical and/ or in vitro assay data. The PBAC also recommended that an additional strength of granules (ivacaftor 25 mg) should be available under Section 100 (Highly Specialised Drugs Program) for use in this population. The PBAC noted that, overall, the evidence supporting the clinical claim in the submission was limited but acknowledged the difficulties in obtaining efficacy data in this population. The PBAC considered it was unlikely ivacaftor would be cost effective at the requested price, 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. However, ivacaftor was likely to be cost effective if it was priced no higher than elexacaftor/ tezacaftor/ ivacaftor (ELX/TEZ/IVA) for the population who would transition to another CFTR modulator at an older age (52% of patients) and for the population for whom there was limited clinical evidence (45% of patients).

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

7.3 The PBAC advised the following with regards to the restriction criteria:

- Removal of the sweat chloride clinical criterion as proposed in the submission was appropriate, noting the more recently listed CFTR modulators do not include this criterion;
- Separate initial and continuing criteria was appropriate, noting all currently listed CFTR modulators include separate criteria; and
- The specific CFTR mutation should be captured in the initial authority application.

7.4 The PBAC considered that the nomination of best supportive care (BSC) 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 CFTR modulators at an older age for some populations (i.e., ivacaftor for

gating population, ELX/TEZ/IVA for F/ any population and tezacaftor/ ivacaftor (TEZ/IVA) for non-F/RF population).

7.5 The PBAC noted the submission presented 8 clinical studies and 3 in-vitro studies to support the clinical claim that ivacaftor is superior to BSC in terms of efficacy. The PBAC noted only one clinical study included CF patients aged 4 months to < 12 months of age (Study 124 in the gating population) with all other studies in older patients. The PBAC noted the mean absolute change in sweat chloride from baseline for the younger patients with a gating mutation was reasonably consistent with that observed in older patients (see paragraph 6.12). For the R117H and RF populations, the PBAC noted the absolute change from baseline in $ppFEV_1$ ranged from 2.1 to 4.7 which did not meet the MCID of ≥ 10 percentage points. The PBAC noted other outcomes showed a numerical benefit for ivacaftor (sweat chloride, BMI, pulmonary exacerbations) but the magnitude of benefit was uncertain. The PBAC noted no clinical data was provided for the population of patients with ivacaftor-responsive mutations. 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.

7.6 The PBAC considered that the claim that ivacaftor had comparable safety to BSC was reasonable, noting that the incidence and type of adverse events 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 considered it unlikely ivacaftor would be cost effective at the requested price, 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 considered ivacaftor was likely to be cost effective for the gating population aged 4 months to 11 months (3% of the additional population) at the ivacaftor price, noting these patients would be eligible to commence treatment with ivacaftor at 12 months of age. The PBAC considered ivacaftor was likely to be cost effective for the remaining population if its unit price was no higher than the unit price of ELX/TEZ/IVA, noting that listing ivacaftor would allow earlier access to a CFTR modulator for 45% of the additional patients that would transition to ELX/TEZ/IVA at an older age and for 7% of the additional patients that would transition to TEZ/IVA at an older age. For the remaining population (45%), the PBAC noted the limited clinical evidence available but considered that it may be reasonable to assume the extent of benefit (and therefore, the cost effectiveness) is similar. The PBAC considered it would be appropriate to implement a weighted effective price across the current and additional ivacaftor populations.

7.8 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. The PBAC considered the use of the updated patient numbers provided in the pre-PBAC response was reasonable.

7.9 The PBAC advised that the net cost of the extended population should be in included in the existing RSA for ivacaftor with the financial caps increased to include the cost of the additional patient population. The PBAC considered a combined RSA for the CFTR modulators, as proposed by the sponsor, was reasonable.

7.10 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 expected to address a high and urgent unmet clinical need for some of the additional population as there are no alternative treatment options;

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.

7.11 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 (ivacaftor 25 mg granules) and amend existing listing (ivacaftor 50 mg and 75 mg granules and 150 mg tablets) as follows:

Amend current ivacaftor restrictions to include the rarer mutations and to expand the age limit. Additions in italics and deletions in strikethrough.

Category / Program: S100 – Section 100 (Highly Specialised Drugs) – Public and Private Hospitals					
MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
IVACAFTOR					
Ivacaftor 25 mg granules, 56 sachets	*NEW HSD (Public) NEW HSD (Private)*	*1*	*56*	*5*	*Kalydeco*
Ivacaftor 50 mg granules, 56 sachets	11105L (Public) 11097C (Private)	1	56	5	Kalydeco
ivacaftor 75 mg granules, 56 sachets	11098D (Public) 11109Q (Private)	1	56	5	Kalydeco

ivacaftor 150 mg tablet, 56 tablets	10170G (Public) 10175M (Private)	1	56	5	Kalydeco
Safety Net Rule Penalty Applies? Yes					
	Administrative Advice: No increase in the maximum number of repeats may be authorised.				
	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				
Initial Restrictions					
Restriction Summary / Treatment of Concept: Authority Required					
	Category / Program: Section 100 – Highly Specialised Drugs Program				
	Prescriber type: ☒Medical Practitioners				
	Restriction Type – ☒Authority Required – non-immediate/delayed assessment by Services Australia				
	Indication: Cystic fibrosis				
	Treatment Phase: Initial treatment – New patients				
	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;~~				
	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 have a sweat chloride value of at least 60 mmol/L by quantitative pilocarpine iontophoresis~~				
	AND				
	Clinical criteria:				
	Patient must not receive more than 24 weeks of treatment under this restriction				
	AND				
	Clinical criteria:				
	The treatment must be given concomitantly with standard therapy for this condition.				
	AND				
	Population criteria:				
	Patient must be aged *4* ~~12~~ months 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.
	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.
	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.
	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 *the specific mutation considered to be responsive to ivacaftor as listed in the TGA approved PI* ~~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 PI* (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.~~
Restriction Summary / Treatment of Concept: Authority Required	
	Category / Program: Section 100 – Highly Specialised Drugs Program
	Prescriber type: ☒Medical Practitioners
	Restriction Type – ☒Authority Required – non-immediate/delayed assessment by Services Australia
	Indication: Cystic fibrosis
	Treatment Phase: Continuing treatment
	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 received PBS-subsidised initial therapy with ivacaftor, given concomitantly with standard therapy, for this condition
	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 *4* ~~12~~ months or older
	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 Continuing Authority Application Supporting Information Form; and (3) current CYP3A4 inhibitors, CYP3A4 inducers and IV antibiotics.

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 positive recommendation by the Pharmaceutical Benefits Advisory Committee (PBAC), to extend the listing of Kalydeco® (ivacaftor) to include:

- patients aged 4-12 months with a gating mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, and

- those aged 4 months 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 data (including patients with R117H, residual function (RF) and rare mutations).

Vertex is committed to working with The Department of Health and Aged Care to enact the recommendation, giving approximately 100 people in Australia access to a medicine to treat the underlying cause of their disease for the first time.