5.09 ELEXACAFTOR WITH TEZACAFTOR AND WITH IVACAFTOR, AND IVACAFTOR

Pack containing 56 sachets elexacaftor 100 mg with tezacaftor 50 mg and with ivacaftor 75 mg and 28 sachets ivacaftor 75 mg

Pack containing 56 sachets elexacaftor 80 mg with tezacaftor 40 mg and with ivacaftor 60 mg and 28 sachets ivacaftor 59.5 mg

Trikafta®,

VERTEX PHARMACEUTICALS (AUSTRALIA) PTY. LTD.

1 Purpose of submission

1.1 The Category 2 submission requested an extension to the current listing of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) for the treatment of cystic fibrosis (CF) in patients who have at least one F508del mutation in the Cystic Fibrosis Transmembrane Regulator (CFTR) gene (herein referred to as the F/any population) to include patients aged 2 to 5 years. The submission identified six populations (aged 2 to 5 years old) who would be eligible for treatment with ELX/TEZ/IVA:

- patients who are homozygous for F508del in the CFTR gene (F/F);
- patients who are heterozygous for F508del in the CFTR gene with a residual function mutation (F/RF);
- patients who are heterozygous for F508del in the CFTR gene with a gating mutation (F/G);
- patients who are heterozygous for F508del in the CFTR gene with a minimal function mutation (F/MF);
- patients who are heterozygous for F508del in the CFTR gene with a R117H mutation (F/R117H); and
- patients who are heterozygous for F508del in the CFTR gene with a second mutation that is unknown or not yet characterised as residual function or minimal function (F/not yet characterised).

1.2 Listing was requested on the basis of: (1) a cost-effectiveness analysis versus lumacaftor/ivacaftor (LUM/IVA) in the F/F population; (2) a cost-effectiveness analysis versus best supportive care (BSC) in the F/MF population; and (3) a cost comparison versus ivacaftor (IVA) in the F/G population. For the F/RF and F/R117H populations,

the submission proposed the same price as currently in place for LUM/IVA. The components of the overall clinical claim addressed by the submission are summarised in Table 1.

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

Component	Description
Population	Patients with CF initiating therapy aged 2 to 5 years who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (F/any)
Intervention	**For patients with CF aged 2 to 5 years inclusive weighing <14 kg:** One sachet of fixed-dose granules containing 80 mg elexacaftor, 40 mg tezacaftor and 60 mg ivacaftor in the morning. One sachet containing 59.5 mg ivacaftor granules in the evening, approximately 12 hours apart. **For patients with CF aged 2 to 5 years inclusive weighing ≥14 kg:** One sachet of fixed-dose granules containing 100 mg elexacaftor, 50 mg tezacaftor and 75 mg ivacaftor in the morning. One sachet containing 75 mg ivacaftor granules in the evening, approximately 12 hours apart.

Comparator	Three comparators:
	• BSC for patients with CF aged 2 to 5 years inclusive who are heterozygous for F508del in the CFTR gene with
	  ○ a minimal function mutation (F/MF)
	  ○ a residual function mutation (F/RF)
	  ○ an R117H mutation (F/R117H)
	  ○ a mutation not yet characterised as RF or MF (F/not yet characterised)
	• Lumacaftor/ivacaftor plus BSC for patients with CF aged 2 to 5 years inclusive who are homozygous for the F508del-CFTR mutation (F/F)
	• Ivacaftor plus BSC for patients with CF aged 2 to 5 years inclusive who are heterozygous for F508del in the CFTR gene with a gating mutation (F/G)

Outcomes	• Absolute change from baseline in: $LCI_{2.5}$; sweat chloride; CFQ-R Respiratory Domain[1] Score; $ppFEV_1$[1]; nutritional status (BMI, BMI-for-age z-score, weight, weight-for-age z-score, height, height-for-age z-score) • Pulmonary exacerbations • Biomarkers (faecal elastase-1 [FE-1], faecal calprotectin, serum immunoreactive trypsinogen [IRT]) • Pharmacokinetic (PK) profile • Safety and tolerability
Clinical claim	For patients with CF aged 2 to 5 years who have at least one F508del mutation in the CFTR gene (F/any), ELX/TEZ/IVA plus BSC is superior in terms of efficacy and comparable in terms of safety compared to the nominated comparator (LUM/IVA plus BSC, IVA plus BSC or BSC alone).

Source: Table 1.1.1 of the submission.

BMI = body mass index; BSC = best supportive care; CF = cystic fibrosis; CFQ-R = Cystic Fibrosis Questionnaire-Revised; CFTR = cystic fibrosis transmembrane conductance regulator; ELX = elexacaftor; F/any = CF patient with at least one F508del mutation in the CFTR gene; F/F = CF patient homozygous for the F508del-CFTR mutation; F/G = CF patient heterozygous for the F508del in the CFTR gene with a gating mutation; F/MF = CF patient heterozygous for the F508del in the CFTR gene with a minimal function mutation; F/not yet characterised = CF patient heterozygous for the F508del in the CFTR gene with the other allele not F508del-CFTR, gating, MF or RF mutation; F/RF = CF patient heterozygous for the F508del in the CFTR gene with a residual function mutation; IVA = ivacaftor; $LCI_{2.5}$ = lung clearance index at 2.5% stopping point; MF = minimal function; $ppFEV_1$ = percent predicted forced expiratory volume in one second; TEZ = tezacaftor; RF = residual function.

1. These two outcomes were not evaluated in the pivotal studies (Study 111 or Study 112) presented in the submission.

1.3 The submission also requested a change to the current listing for ELX/TEZ/IVA to include patients (aged ≥ 2 years) with any mutation that is responsive to ELX/TEZ/IVA. The PBAC noted this population is outside of the current approved Therapeutic Goods Administration (TGA) indication for ELX/TEZ/IVA and a proposed change to the indication to include patients with 'a mutation in the CFTR gene that is responsive based on in vitro data' was not supported by the TGA Advisory Committee on Medicines (ACM) in August 2022. The PBAC noted the pre-PBAC response indicated a

submission seeking registration for patients with responsive mutations was provided to the TGA in February 2024. The PBAC noted some clinical data for this population was provided but considered it was not appropriate to review at this time given the TGA timelines. The PBAC would welcome a submission requesting PBS listing for this population at the appropriate time.

2 Background

Registration status

2.1 ELX/TEZ/IVA is approved by the Therapeutic Goods Administration (TGA) for the treatment of CF in patients aged 6 years and older who have at least one F508del mutation in the CFTR gene.

2.2 This submission to the PBAC to extend the population to include patients aged 2 years and older was made under the TGA/ PBAC parallel process pathway. The TGA Delegate's Overview and ACM minutes were provided during evaluation, with TGA approval on 7 February 2024.

Previous PBAC consideration

2.3 The PBAC has previously considered a number of submissions to extend the PBS age restrictions for CFTR modulators, as summarised in Table 2.

Table 2: First PBAC recommendation for CFTR modulators in CF

	Lumacaftor/ ivacaftor	Ivacaftor	Elexacaftor/tezacaftor/ ivacaftor	Tezacaftor/ ivacaftor
PBS population	F/F	At least one G551D mutation or at least one Class III mutation	F/any	F/F or at least one RF mutation
First recommended by PBAC	Aged ≥ 12 years: July 2018 Aged 6 to 11 years: July 2018 Aged 2 to 5 years: July 2019 Aged 1 to < 2 years: July 2023	Aged ≥ 6 years: November 2013 Aged 2 to 5 years: January 2017 Aged 1 to < 2 years: March 2019 Aged 4 months to < 1 year[1]: November 2023	Aged ≥ 12 years: July 2021 Aged 6 to 11 years: November 2022 Aged 2 to 5 years: current submission	Aged ≥ 12 years: March 2019

CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane regulator; PBAC = pharmaceutical benefits advisory committee.

1. Recommended for patients aged 4 months or older with at least one mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/ or in vitro assay data. This population was not PBS listed at the time of PBAC consideration.

3 Requested listing

3.1 The submission requested two new presentations: a new strength in granule form, ELX 80 mg/TEZ 40 mg/IVA 60 mg and IVA 59.5 mg, for patients weighing ≤ 14 kg and a

granule form of the ELX 100 mg/TEZ 50 mg/IVA 50 mg and IVA 75 mg dose in a 56 sachet pack size (this dose is currently PBS listed in tablet form with a pack size of 84).

3.2 The sponsor proposed a Special Pricing Arrangement for ELX/TEZ/IVA at the currently agreed effective price.

Name, restriction, manner of administration, form	Maximum quantity (units)	Number of repeats	Dispensed price for maximum quantity [$SPA]	Proprietary name and manufacturer
Elexacaftor 100 mg/ tezacaftor 50 mg/ ivacaftor 75 mg granules co-packaged with ivacaftor 75 mg granules	Pack containing 56 sachets (4-week supply)	5	Published (private): $21,375.00 Published (private): $21,423.37 Effective (public): $[redacted] Effective (private): $[redacted][a]	Trikafta®, Vertex Pharmaceuticals (Australia) Pty Ltd
Elexacaftor 80 mg/ tezacaftor 40 mg/ ivacaftor 60 mg granules co-packaged with ivacaftor 59.5 mg granules	Pack containing 56 sachets (4-week supply)	5	Published (private): $21,375.00 Published (private): $21,423.37 Effective (public): $[redacted] Effective (private): $[redacted][a]	Trikafta®, Vertex Pharmaceuticals (Australia) Pty Ltd
Category / Program: Section 100 – Highly Specialised Drugs Program [Public and Private Hospitals]				
Prescriber type: Medical Practitioners				
Restriction type: Authority Required – written non-immediate/delayed assessment by Services Australia				
Indication: Cystic fibrosis				
Treatment Phase: Initial/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				
AND				
Clinical criteria:				
Patient must have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance (*CFTR*) gene				
AND				
Clinical criteria:				
The treatment must be given concomitantly with standard therapy for this condition.				
AND				
Clinical Criteria:				
Patient must have either chronic sinopulmonary disease or gastrointestinal and nutritional abnormalities, prior to initiating treatment with this drug				
AND				
Population criteria:				
~~Patient must be 2 years of age or older~~. *Patient must be 2 to 5 years of age*				
Prescribing Instructions:				
This pharmaceutical benefit is not PBS-subsidised for this condition in a patient who is currently receiving one of the strong CYP3A4 inducers outlined in the Product Information.				
Prescribing Instructions:				
The authority application must be in writing and must include: (1) a completed authority prescription; and (2) a completed Cystic Fibrosis Authority Application Supporting Information Form; and (3) details of the pathology report substantiating the patient having at least one *F508del* mutation - 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				
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.				
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. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
Administrative Advice: For the purposes of this restriction, CFTR modulators, regardless if they are available as a single drug or in combination, are currently: elexacaftor, ivacaftor, lumacaftor, tezacaftor.
Administrative Advice: Special Pricing Arrangements apply.

Source: Table 1.4.3 pp28-29 of the submission
a calculated during the evaluation as the public effective price plus the PBS ready dispensing fee and $40 mark-up.

3.3 The submission listed all presentations of ELX/TEZ/IVA under the same criteria with the clinical criteria: 'Patient must be 2 years of age or older'. However, the granules are only relevant for children aged 2 to 5 years of age. To avoid inadvertent use of the two granule formulations beyond the recommended age groups, the Secretariat has proposed the criterion: 'Patient must be at least 2 to 5 years of age' be included for the granules. The Pre-Sub-Committee Response (PSCR) stated it was agreeable to the inclusion of these criteria.

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 ELX/TEZ/IVA increases both the quantity and function of CFTR protein. ELX/TEZ/IVA is a combination therapy that includes two classes of CFTR modulators, potentiators and correctors, with complementary mechanisms of action. ELX and TEZ are both CFTR correctors that work by facilitating the cellular processing and trafficking of normal and multiple mutant forms of CFTR, including F508del-CFTR, thereby increasing the quantity of functional CFTR protein at the cell surface, resulting in enhanced chloride transport. IVA is a CFTR potentiator that increases the channel-open probability (or gating) of CFTR at the cell surface to enhance chloride transport. IVA can potentiate the function of the CFTR protein delivered to the cell surface by ELX and TEZ, leading to further enhancement of chloride transport than achieved with either agent alone.

4.3 In 2021, there were 308 people with CF aged between 2 to 5 years. The ACFDR report 2021 does not explicitly state how many children between the ages of 2 to 5 had the F508del mutation, but it does state that 47.0% of people with CF were homozygous

and 43.0% were heterozygous for F508del i.e., 90.0% have at least one F508del variant.[1]

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

5 Comparator

5.1 This submission nominated three main comparators for efficacy and safety based on the patient's mutation on the other allele.

- For the F/F population aged 2 to 5 years, the main comparator is LUM/IVA.
- For the F/G population aged 2 to 5 years, the main comparator is IVA.
- For the F/MF, F/RF, F/R117H and F/not yet characterised population aged 2 to 5 years, there is currently no PBS-listed CFTR modulator available. In these patient populations the submission proposed BSC as the main comparator. At the November 2023 PBAC meeting, the PBAC made a positive recommendation for the listing of IVA for patients with a CF mutation that is responsive to IVA in vitro (para 8.1, Ivacaftor, Ratified Minutes, November 2023 PBAC Meeting). Thus, IVA if PBS listed would be the appropriate comparator, rather than BSC, for the F/RF, F/R117H and a proportion of the F/not yet characterised populations. These comparisons were not addressed by the submission.

5.2 The PBAC has previously accepted the nominated comparators listed above for patients aged 6 to 12 years, (para 5.4, ELX/TEZ/IVA Public Summary Document (PSD), November 2022 PBAC meeting with March 2023 Addendum). However, given treatment is ongoing for the lifetime of the patient the more relevant comparators are:

- LUM/IVA from 2 to 5 years of age followed by ELX/TEZ/IVA from 6 years of age in the F/F population;
- IVA from 2 to 5 years of age followed by ELX/TEZ/IVA from 6 years of age in the F/G population; and
- BSC from 2 to 5 years of age followed by ELX/TEZ/IVA from 6 years of age in the F/RF, F/R117H, F/MF and F/not yet characterised population.

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 clinician discussed historical data on the decline of lung function without effective treatments and the need to prevent

[1] Australia Cystic Fibrosis Data Registry – Annual Report 2021

early changes in young children 2 to 5 years old, noting that the first five years of life are critical in setting the trajectory for progressive lung disease in adolescence. The clinician stated that access to ELX/TEZ/IVA will lead to improvements in long term health outcomes for this patient group. The clinician showed the relationship between sweat chloride (SwCl) measurements and lung/pancreatic function (<30 mmol/L corresponds with normal airways and pancreatic function, whereas 30–60 mmol/L corresponds with airway thickening and only 50% pancreatic function).

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (359), health care professionals (8) and one organisation via the Consumer Comments facility on the PBS website.

6.3 Cystic Fibrosis Australia noted the clinical data supported the safety and efficacy of ELX/TEZ/IVA in children aged 2 to 5 years. The comments stressed the importance of starting treatment with CFTR modulators at a young age to support better outcomes, including improved quality of life, for individuals with CF. The comments noted there is also a benefit that extends to carers and siblings of children with CF.

6.4 Several health care professionals emphasised the importance of early treatment with ELX/TEZ/IVA in patients between 2 to 5 years old to prevent irreversible lung damage, reduce severity of infections, increase life expectancy, and decrease mortality rates. The clinicians emphasised that the irreversible lung damage that occurs in the 2 to 5 age group from CF has lifelong implications. The clinicians also discussed that ELX/TEZ/IVA would have a positive impact on growth and development with enhanced nutritional status.

6.5 The comments from individuals to support ELX/TEZ/IVA listing were received from CF patients (both current/potential ELX/TEZ/IVA patients) and family members/carers. In addition to the comments provided by health care professionals, individual comments focused on improvements in lung function, reduced fatigue, and quicker recovery from infections. Many respondents who do not have access expressed hope that ELX/TEZ/IVA will prevent any further lung damage, reduce mucus build up, and negate the need for lung transplants and prolonged antibiotic use.

6.6 The PBAC noted that the advice from health care professionals, individuals and the organisation was supportive of the evidence provided in the submission.

Clinical studies

6.7 There were no head-to-head randomised trials available comparing ELX/TEZ/IVA plus BSC with the nominated comparators for the requested ages. The submission presented one 24-week single arm trial in patients 2 to 5 years of age evaluating the safety and efficacy of ELX/TEZ/IVA granules in patients with F/F and F/MF genotypes, Study 111 (Part A (N=18); Part B (N=75)), and one open-label extension (OLE) of Study 111 that evaluated the long-term safety and efficacy of ELX/TEZ/IVA granules in patients with F/F and F/MF genotypes, Study 112 (N=70).

6.8 The submission also presented 3 single-arm OLE studies that evaluated the long-term safety and efficacy of ELX/TEZ/IVA in patients with the F/F and F/MF genotypes (Study 105, N=506, Study 107, N=64) and in patients with the F/MF genotype only (Study 119, N=120). Study 107 and Study 119 were conducted in patients aged ≥ 6 years whereas Study 105 was conducted in patients aged ≥ 12 years. The submission also presented the MAGNIFY study, a non-interventional, observational study evaluating the quality of life (QoL) in patients commencing LUM/IVA, TEZ/IVA or ELX/TEZ/IVA, and the caregivers of patients using the aforementioned therapies. The submission focused on the QoL reported in patients using ELX/TEZ/IVA and caregivers of patients using ELX/TEZ/IVA.

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

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Study 111 VX20-445-111	Clinical Study Report, A Phase 3 Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Elexacaftor/Tezacaftor/Ivacaftor Triple Combination Therapy in Cystic Fibrosis Subjects 2 Through 5 Years of Age. Version 1.0; 15 Sept 2022. Vertex Data on File. VX20-445-111 KRM & 2-5 Value Deliverables Update Slide Deck (16 November 2022). Goralski JL, *et al.* Phase 3 Open-Label Clinical Trial of Elexacaftor/Tezacaftor/Ivacaftor in Children Aged 2-5 Years with Cystic Fibrosis and at least One F508del Allele.	NCT04537793 *Am J Respir Crit Care Med* 2023; 208: 59-67.
Study 112 VX20-445-112	Study VX20-445-112 Week 48 Interim Analysis Key Results Vertex Data on File. VX20-445-112 Week 48 IA Key Results Memo Slide Deck (01 June 2023). (REF-21100).	NCT05153317
Study 105 VX17-445-105	Polineni D, et al. Long-term Safety and Efficacy of Elexacaftor/ Tezacaftor/ Ivacaftor (ELX/TEZ/IVA) in People With Cystic Fibrosis (CF) and At Least One F508del Allele: An Open-Label, 192 Week Extension Study. Presented at the 46th European Cystic Fibrosis Conference; 7-10 June 2023. Lee, T., et al. Effect of elexacaftor/tezacaftor/ivacaftor on annual rate of lung function decline in people with cystic fibrosis.	NCT03525574 Journal of Cystic Fibrosis 2023; 22(3): 402-406.
Study 107 VX19-445-107	Vertex Data on File. Study VX19-445-107 Week 144 Interim Analysis Key Results (REF-20999). Vertex Data on File. 445-107 Week 144 Interim Analysis Key Results Memo Slide Deck (03 May 2023).	NCT04183790
Study 119 VX20-445-119 NCT04545515	Abbreviated Clinical Study Report, A Phase 3b Open-label Study Evaluating the Long-term Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor Combination Therapy in Cystic Fibrosis Subjects Ages 6 Years and Older Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF). Version 1.0; 18 September 2023.	
MAGNIFY Study	Thia LP, et al. Real-World Impact of ELX/TEZ/IVA on Quality of Life of Children With CF Aged 6-11 Years and Primary Caregivers in the UK: MAGNIFY, a Prospective, Observational, Non-interventional Study. Presented at the 46th European Cystic Fibrosis Conference; 7-10 June 2023 (Poster 118).	

Source: Table 2.2.1 p38 of the submission.
CF = cystic fibrosis; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; F/MF = CF patient heterozygous for the F508del in the CFTR gene with a minimal function mutation.

6.10 The key features of the trials are summarised in Table 4. Both pivotal trials (Study 111 and Study 112) were relatively short (Study 111, 24 weeks; Study 112, 48-week interim analysis (IA) available) in the context of a chronic therapy. Study 111, Study 112 and Study 107 had small sample sizes (n=75, n=70 and n=64, respectively). All of the studies were non-comparative by design. The single arm nature, short-duration and small sample sizes render these studies vulnerable to confounders and uncertainty in effects.

6.11 The mean (SD) ages reported in Study 111 and Study 112 were 4.1 (1.1) and 4.1 (1.0), respectively. The minimum age in both studies was 2.1 years and the maximum age was 6.0 years. In Study 111, 14.7% of patients were aged ≥ 2 to < 3 years, 36.0% of patients were aged ≥ 3 to < 4 years, 29.3% were aged ≥4 to <5 years and 20.0% of patients were aged ≥5 to <6 years. The age distribution in Study 111 reflected the requested PBS population.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Aged 2 to 5 years						
Study 111	Part A: 18 Part B: 75	OL, 24 weeks	High	F/F, F/MF aged 2 to 5 years	Part A: Primary: pharmacokinetics, safety Part B: Primary: safety, pharmacokinetics Secondary: SwCl, $LCI_{2.5}$ Other: faecal calprotectin, FE-1, IRT, BMI, weight, height, PEx	Adverse effects
Study 112	70	OL, 48 weeks	High	F/F, F/MF aged 2 to 5 years	Primary: Safety and tolerability Secondary SwCl, $LCI_{2.5}$, growth parameters, (weight, height, BMI) and biomarkers (FE-1, faecal calprotectin, IRT) and $ppFEV_1$	Not used
Aged ≥ 6 years						
Study 105	506	OL, 192 weeks	High	F/F, F/MF aged ≥ 12 years	Primary: safety and tolerability Secondary: $ppFEV_1$, SwCl, PEx, BMI and CFQ-R respiratory domain	Annualised mean rate of change in $ppFEV_1$
Study 107	64	OL, 144 weeks	High	F/F, F/MF aged ≥ 6 years	Primary: safety and tolerability Secondary: $ppFEV_1$, CFQ-R score, growth parameters (height, BMI and corresponding z-scores), $LCI_{2.5}$, PEx and CF-related hospitalisations	Not used
Study 119	120	OL, 192 weeks	High	F/F, F/MF aged ≥ 6 years	Primary: safety and tolerability Secondary: SwCl, $LCI_{2.5}$ Other: $ppFEV_1$, CFQ-R respiratory domain,	Not used

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
MAGNIFY	PRO, n=27 CGRO=25	The mean duration of follow-up in PRO analysis set at the IA: 17.8 The mean duration of follow-up in CGRO analysis set at the IA: 17.5	NA	Patients aged 6 to 11 years AND Part A: Patients with CF receiving treatment with LUM/IVA or TEZ/IVA and caregivers of patients treated with LUM/IVA or TEZ/IVA Part B: Patients with CF receiving treatment with ELX/TEZ/IVA and caregivers of patients treated with ELX/TEZ/IVA	CFQ-R CarerQoL 7D CarerQoL-VAS SF-12 WPAI+CIQ:SHP	Carer utility applied

Source: developed during the evaluation, pp42-91 of the submission; pp19-26 Study 119 CSR, Table 9.5.2 p24 VX20-CFD-004 IA CSR.
BMI = body mass index; CarerQoL 7D = Care-Related Quality of Life of Caregivers; CarerQoL VAS = Care Related Quality of Life - visual analog scale; CFQ-R = cystic fibrosis questionnaire revised; CGRO = caregiver reported outcome; ELX = elexacaftor; FE-1 = faecal elastase-1; F/MF = CF patient heterozygous for the *F508del* in the *CFTR* gene with a minimal function mutation; F/RF = CF patient heterozygous for the *F508del* in the *CFTR* gene with a residual function mutation; IRT = immunoreactive trypsinogen; IVA = ivacaftor; $LCI_{2.5}$ = lung clearance index at 2.5% stopping point; LUM = lumacaftor; NA = not applicable; OL = open label; OLE = open label extension; PEx = pulmonary exacerbations; $ppFEV_1$ = per cent predicted forced expiratory volume in one second; PRO = patient reported outcomes; QoL = quality of life; SF-12 = 12-Item Short Form Health Survey; SwCl = sweat chloride; TEZ = tezacaftor; WPAI+CIQ:SHP = Work Productivity and Activity Impairment plus Classroom Impairment Questionnaire: Specific Health Problem.

Comparative effectiveness

6.12 The primary outcome in all of the studies presented in the submission was safety and tolerability. The PBAC has previously considered $ppFEV_1$ as the outcome of interest in patients with CF aged ≥ 2 years. Study 111 and Study 112 did not assess $ppFEV_1$. This was reasonable given the difficulty in conducting spirometry in the younger population and the limited interpretability of this outcome given the relatively good lung function in the younger cohort. The submission presented a number of pharmacodynamic (PD) outcomes as a measure of efficacy. Results for these secondary and other efficacy endpoints for Study 111 and Study 112, as outlined in Table 4, are described below.

Patients aged 2 to 5 years with an F/F or F/MF mutation

6.13 Based on the results from Study 111, treatment with ELX/TEZ/IVA over 24 weeks in CF patients aged 2 to 5 years with an F/F or F/MF mutation resulted in an improvement in the secondary and other efficacy endpoints from baseline. The findings are summarised in Table 5. These outcomes were sustained at the OLE, Study 112 48-week IA.

6.14 With respect to SwCl, the absolute change from baseline through Week 24 fell below the threshold for diagnosing CF, thereby meeting the minimum clinically important difference (MCID) definition proposed by the submission. SwCl fell by 57.5% thereby meeting the National health Service (NHS) definition for response to IVA treatment,

which has previously been considered in submissions for other CFTRs (lumacaftor/ivacaftor PSD, July 2023 PBAC Meeting). At the 48-week OLE, the reduction from baseline in SwCl observed at 24 weeks was maintained. The PBAC has previously considered a reduction in SwCl as evidence of biological activity (para 6.22, ivacaftor PSD, March 2019 PBAC meeting) for CFTR modulators in the treatment of patients with CF. In the absence of comparative data, the ESC previously considered that given the aetiology of CF and the results of intermediate outcomes (including reduction in sweat chloride), the claim of superior efficacy compared with BSC alone was biologically plausible (para 6.19, lumacaftor/ivacaftor PSD, July 2019 PBAC Meeting).

6.15 With respect to $LCI_{2.5}$, an improvement (reduction) in the absolute change from baseline through Week 24 was observed. At the 48-week OLE, a further reduction in $LCI_{2.5}$ was observed. Statistical significance for this outcome at this time point was not reported. The submission did not nominate an MCID for this outcome. The impact of the improvement in $LCI_{2.5}$ in terms of improvements in survival or quality of life is uncertain (para 6.36, lumacaftor/ivacaftor PSD, July 2018 PBAC Meeting).

6.16 With respect to nutritional parameters and biomarkers, patients in Study 111 gained weight and height. Other growth parameters, including weight-for-age z-score, remained stable over the study period. Improvements in pancreatic and inflammatory biomarkers were observed, although most patients (n=69, 92%) displayed pancreatic insufficiency at the end of the study period. At the 48-week OLE, weight, height and BMI z-scores continued to remain stable, but 57 (81.4%) patients still displayed pancreatic insufficiency.

Table 5: Summary of the efficacy endpoints in Study 111 and Study 112.

	Study 111			Study 112	
Outcome definition	**N at week 24**	**Descriptive summary**	**LS mean (SE), 95%CI absolute change from baseline at week 24**	**N at 48-week OLE**	**LS Mean (SE), 95% CI of LS mean absolute change at OLE Part A Week 48**
SwCl (mmol/L)	69	SwCl decreased over the 24-week treatment period and this effect was sustained at the 48-week OLE.	-57.9 (1.7) (-61.3, -54.6)	56	-59.21 (2.1) (-63.3, -54.8)
$LCI_{2.5}$	50	$LCI_{2.5}$ decreased over the 24-week study period and this reduced further at the 48-week OLE.	-0.83 (0.09) (-1.01, -0.66)	34	-0.97 (0.16) (-1.29, -0.65)

	Study 111			Study 112	
Outcome definition	**N at week 24**	**Descriptive summary**	**LS mean (SE), 95%CI absolute change from baseline at week 24**	**N at 48-week OLE**	**LS Mean (SE), 95% CI of LS mean absolute change at OLE Part A Week 48**
FE-1 levels at Week 24 (mg/g)	54	FE-1 improved over 24 weeks of treatment. At week 24 only 6 children had FE-1 levels above 200 mg/g (the threshold for pancreatic insufficiency) compared to 2 patients at baseline. At week 48 OLE, 13 patients had FE-1 levels above 200 mg/kg.	39.5 (89.2)[a]	53	89.8 (139.0)[a]
Serum IRT levels at Week 24 (µg/L)	70	The serum IRT levels decreased over 24 weeks of treatment.	-166 (285.0) [a]	NR	NR
Faecal calprotectin mg/kg	52	Faecal calprotectin levels reduced over the 24-week study period	-289.66 (719.22) [a]	NR	NR
Weight (kg)	75	Weight gain was observed during the study.	1.0 (0.1) (95% CI: 0.9, 1.2)	NR	NR
Weight-for-age z score	75	Mean weight-for-age z-score remained stable during the study	0.02 (0.03) (95% CI: -0.04, 0.09)	67	-0.01 (0.05) (-0.11, 0.08)
Height (cm)	75	A small gain in length was observed during the study.	3.1 (0.1) (95% CI: 2.8, 3.3)	NR	NR
Height-for-age z-score	75	Height-for-age z-score remained stable during the study.	-0.06 (0.03) (95% CI: -0.11, 0.00)	67	-0.12 (0.04) (-0.19, -0.04)
BMI (kg/m^2)	75	BMI remained stable during the study	0.03 (0.07) (95% CI: -0.10, 0.17)	NR	NR
BMI-for-age z-score	75	BMI-for-age z-score remained stable during the study	0.10 (0.05) (95% CI: 0.00, 0.20)	67	0.09 (0.05) (-0.02, 0.20)
Number of PEx	75	There were 12 (16.0%) patients with a PEx event. There were 12 total PEx events. The observed event rate per year was 0.32.	NR	70	There were 27 (36.0%) patients with a PEx. There were 68 total events. The observed event rate per year was 0.56.

Source: Table 2.5.5, p57; Table 2.5.6, pp59-60; Table 2.5.7, p61 of the submission; Table 11-3 p71, Table 11-4 p73, Table 14.2..5.1.1b pp241-242 Study 111 CSR. Study 112: Table 14.2.1.2a pp50-51, Table 14.2.2.2a pp52-53, Table 14.2.4.4a pp54-56; Table 14.2.5.4a pp57-59; Table 14.2.3.4a pp60-62; Table 14.2.7.1.1a p63; Table 14.2.6.1a p65; Study 112 WK48 IA.

BMI = body mass index; CF = cystic fibrosis; FAS = Full Analysis Set; FE-1 = faecal elastase-1; IRT = immunoreactive trypsin; IVA = ivacaftor; $LCI_{2.5}$ = lung clearance index at 2.5% stopping point; NR = not reported; OLE = open label extension; PEx = pulmonary exacerbations; SD = standard deviation; SwCl = sweat chloride.

a mean (SD) reported.

Evidence in older age groups (supportive evidence)

6.17 The submission presented 3 studies to support the long-term use of ELX/TEZ/IVA (Study 105, Study 107 and Study 119). These studies were conducted in patients aged ≥ 12 years (Study 105) and ≥ 6 years (Study 107 and Study 119).

6.18 Study 105 demonstrated improvements in $ppFEV_1$, SwCl, BMI and CFQ-R RD from the parent study baseline measures following treatment with ELX/TEZ/IVA in patients who switched from TEZ/IVA or placebo in the parent studies, and maintenance or improvement in the efficacy outcomes for patients originally allocated to ELX/TEZ/IVA in the parent study. It is unclear whether these results, in terms of change in $ppFEV_1$ observed, would be replicated in the younger age group who are in a different stage of pathology (i.e., likely to have normal lung function).

6.19 At the 144-week IA for Study 107, an improvement from the parent study baseline was observed for all outcomes. However, when comparing to the parent study week-24 analysis, a decline in SwCl, $ppFEV_1$ and CFQ-R RD, and an improvement in BMI, and $LCI_{2.5}$ at OLE week-144 was observed.

6.20 In Study 119, an improvement in all outcomes ($ppFEV_1$, SwCl, $LCI_{2.5}$ and CFQ-R RD) from the parent study baseline to week 96 of the OLE was observed for patients who were originally allocated to placebo. When comparing to the parent study week-24 analysis, patients originally allocated to ELX/TEZ/IVA experienced a small improvement in SwCl and $LCI_{2.5}$, but demonstrated a decline in $ppFEV_1$ and CFQ-R RD, noting the relatively good $ppFEV_1$ (>87%) at parent study baseline for both arms.

6.21 The submission did not present any translation studies to show how outcomes for older patients could be applied to generate outcomes for younger patients. Results for Study 105, Study 107 and Study 119 are summarised in Table 6.

Table 6: Summary of the efficacy endpoints in Study 105, Study 107 and Study 119

Outcome	Study 105 (ELX/TEZ/IVA)[a]				Study 107[b]	Study 119[c]	
	PBO in Study 102	ELX/TEZ/IVA in Study 102	TEZ/IVA in Study 103 N = 52	ELX/TEZ/IVA in Study 103 N = 55	ELX/TEZ/IVA	PBO in Study 116 N = 61	ELX/TEZ/IVA in Study 116 N = 60
Absolute change from parent study baseline in $ppFEV_1$ (percentage points)							
n	136	133	32	36	27	41	38
LS mean (SE) 95% CI	15.3 (0.8) (13.7, 16.8)	13.8 (0.8) (12.3, 15.4)	10.9 (1.3) (8.2, 13.6)	10.7 (1.3) (8.1, 13.3)	10.1 (2.0) (6.0, 14.1)	6.1 (1.8) (2.6, 9.7)	6.9 (1.9) (3.2, 10.5)
Absolute change from parent study baseline in SwCl (mmol/L)							
n	133	128	31	38	37	52	46
LS mean (SE) 95% CI	-47.0 (1.6) (-50.1, -43.9)	-45.3 (1.6) (-48.5, -42.2)	-48.2 (3.8) (-55.8, -40.7)	-48.2 (3.5) (-55.1, -41.3)	-58.5 (2.4) (-63.4, -53.6)	-57.3 (2.4) (-61.6, -52.9)	-57.5 (2.3) (-62.0, -53.0)
Absolute change from parent study baseline in $LCI_{2.5}$							
n	NR	NR	NR	NR	28	56	48
LS mean (SE) 95% CI	NR	NR	NR	NR	-2.17 (0.30) (-2.78, -1.56)	-1.74 (0.18) (-2.09, -1.38)	-2.35 (0.19) (-2.72, -1.97)
Absolute change from parent study baseline in CFQ-R RD score (points)							
n	148	147	33	42	38	56	54
LS mean (SE) 95% CI	15.3 (1.5) (12.3, 18.3)	18.3 (1.5) (15.3, 21.3)	14.8 (2.6) (9.7, 20.0)	17.6 (2.4) (12.8, 22.4)	8.7 (2.0) (4.6, 12.8)	6.6 (2.1) (2.5, 10.8)	2.6 (2.1) (-1.6, 6.8)
Absolute change from parent study baseline in BMI score (points)							
n	144	139	32	42	42	NR	NR
LS mean (SE) 95% CI	1.81 (0.16) (1.50, 2.12)	1.74 (0.16) (1.43, 2.05)	1.72 (0.24) (1.25, 2.19)	1.85 (0.22) (1.41, 2.28)	2.86 (0.28) (2.31, 3.42)	NR	NR
PEx							
Patients with events	174 (43.2)		43 (40.2)		8 (12.1)	NR	NR
Events n	385		71		10	NR	NR
Event rate per year	0.21 (0.17, 0.25)		0.18 (0.12, 0.25)		0.047	NR	NR

Source: Table 11-2 pp46-47, Study 105 Final Week 192 and Extension Period CSR; Table 2.6.9 p81 of the submission; Table 11-1, pp19-20, Table 11-2, p22, Table 11-3, pp24-25, Table 11-4, p26, Study 119 CSR.

BMI = body mass index; CFQ-R RD = Cystic Fibrosis Questionnaire-Revised Respiratory Domain; CI = confidence interval; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; IVA = ivacaftor; $LCI_{2.5}$ = lung clearance index at 2.5% stopping point; LS = least squares; n = size of subsample; N = total parent study FAS sample size; OL = open-label; PBO = placebo; PEx = pulmonary exacerbation; $ppFEV_1$ = percent predicted forced expiratory volume in 1 second; SE = standard error; SwCl = sweat chloride.

a at OL Week 192

b at OL Week 144

c at OL Week 96

Patients with CF aged 6 to 11 years and caregivers of patients with CF aged 6 to 11 years

6.22 The submission presented the results of an interim analysis of the MAGNIFY study that assessed QoL in children with CF aged 6 to 11 years and the burden on caregivers. For patients using ELX/TEZ/IVA (Part B), the study reported a numerical increase in the CFQ-R RD score. The mean (SD) follow-up duration was 124.8 (26.3) days. The mean (SD) change from baseline was 6.2 (12.6). For caregivers of patients using ELX/TEZ/IVA the study reported a numerical increase in the CarerQOL-7D utility score. The mean (SD) follow-up duration was 122.2 (34.3) days. The mean (SD) change from baseline was 3.43 (6.38). The CarerQOL-7D utility score was used in the economic model.

Comparative harms

6.23 The submission did not present a comparison of safety outcomes for ELX/TEZ/IVA + BSC versus any of the nominated comparators.

Study 111 Part A

6.24 Study 111 Part A was 15 days in duration with a safety follow-up visit 28 days after the last dose. The majority of patients experienced mild to moderate adverse events (AEs) that were typical of CF patients and consistent with the safety profile of ELX/TEZ/IVA. Three (16.7%) patients experienced elevated alanine transferase (ALT). Two (11.1%) patients experienced elevated aspartate transferase (AST). All of these events were mild to moderate in severity and did not lead to study drug interruption or discontinuation.

Study 111 Part B

6.25 Study 111 Part B was 24 weeks in duration with a safety follow-up visit 28 days after the last dose. One participant had a serious adverse event (SAE) of abnormal behaviour that resolved after ELX/TEZ/IVA was discontinued. This was assessed to be possibly related to ELX/TEZ/IVA, noting that the patient had a history of behavioural and development issues. Another patient had an SAE of PEx. This is a clinical manifestation of CF. Eight (10.7%) patients experienced elevated ALT and 4 (5.3%) patients experienced elevated AST. Elevated transaminases led to treatment interruption for 1 (1.3%) patient in Part B.

Study 112

6.26 At the Study 112 48-week IA, 69 (98.6%) patients experienced an AE. The majority of AEs were mild to moderate in severity. Five (7.1%) events were severe (noting that patients in this study were rollover patients from Study 111 and hence, the higher incidence of SAEs is associated with longer term exposure). The submission did not provide any detail of these severe AEs. Thirteen (18.6%) patients experienced an SAE, although it was only found to be related to study drug for 1 (1.4%) patient. No further details regarding this patient or event were provided. Treatment was discontinued in 2 (2.9%) patients due to an AE; 1 event was due to elevated transaminases (p33, Study 112 WK48 IA). Details for reasons for discontinuation for the other patient were not provided. Study drug was interrupted in 3 (4.3%) patients. Five (7.1%) patients experienced elevated ALT/AST levels.

6.27 Overall, ELX/TEZ/IVA was generally safe and well tolerated in patients with F/F or F/MF genotypes aged 2 to 5 years. No deaths were reported in either group in either part of the study or in the OLE. A summary for the AEs reported in Study 111 and Study 112 are presented in Table 7.

Table 7: Overview of adverse effects in Study 111 Part A and Part B, Safety Set, and Study 112

	ELX/TEZ/IVA		
	Study 111		Study 112
	Part A (N=18)	Part B (N=75)	N = 70
Participants with AEs	15 (83.3)	74 (98.7)	69 (95.6)
AEs by maximum severity Mild Moderate Severe	 12 (66.7) 3 (16.7) 0	 47 (62.7) 27 (36.0) 0	 32(45.7) 32 (45.7) 5 (7.1)
AEs by strongest relationship Not related Unlikely related Possibly related Related	 5 (27.8) 5 (27.8) 4 (22.2) 1 (5.6)	 15 (20.0) 27 (36.0) 32 (42.7) 0	 26 (37.1) 26 (37.1) 15 (21.4) 2 (2.9)
Serious AEs	0	2 (2.7)	13 (18.6)
Related serious AEs	0	1 (1.3)	1 (1.4)
Grade 3/4/5 AEs	0	0	5 (7.1)
AEs leading to discontinuation	0	1 (1.3)[b]	2 (2.9)
AEs leading to interruption	1 (5.6)[a]	5 (6.7)	3 (4.3)

Source: Table 2.5.9 p58, of the submission; Table 14.3.1.1a pp14-15 Study 112 WK48 IA

AE = adverse event; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor.

[a] One child interrupted treatment on Day 3 for 1 day due to non-serious AEs of hyperamylasemia and hyperlipasemia that were mild in severity, were not considered to be related to study drug, and which resolved;

[b] one child had an AE of abnormal behaviour, which resolved after ELX/TEZ/IVA discontinuation.

Subjects with multiple events within a category is counted multiple times in that category.

6.28 No critical safety concerns were raised by additional longer-term data in Study 105, Study 107 of Study 119. A summary of the AEs in the OLEs is shown in Table 8. The TGA Clinical Evaluation Report (CER) noted the number of AEs and severe AEs in Study 105, particularly the rate of raised transaminases, rash and incidence of AEs generally. However, they concluded that these are known risks of ELX/TEZ/IVA and documented in the Risk Management Plan (TGA Clinical Evaluation Report, September 2023).

6.29 The submission did not present any safety data for the F/RF, F/R117H, F/G populations.

Table 8: Summary of the adverse events reported in Study 106, 107 and 119, Safety Sets.

	Study 106 192-week analysis ELX/TEZ/IVA (N=506)	Study 107 144-week IA ELX/TEZ/IVA (N=64)	Study 119 96-week IA ELX/TEZ/IVA (N=120)
	Participants, n (%)	Participants, n (%)	Participants, n (%)
All AEs	504 (99.6)	64 (100.0)	118 (98.3)
AEs by maximum severity			
Mild	65 (12.8)	23 (35.9)	52 (43.3)
Moderate	307 (60.7)	39 (60.9)	58 (48.3)
Severe	125 (24.7)	2 (3.1)	8 (6.7)
Life-threatening	7 (1.4)	0	0
AEs by strongest relationship			
Not related	121 (23.9)	20 (31.3)	30 (25.0)
Unlikely related	133 (26.3)	20 (31.3)	32 (26.7)
Possibly related	226 (44.7)	24 (37.5)	55 (45.8)
Related	24 (4.7)	0	1 (0.8)
SAEs	175 (34.6)	5 (7.8)	13 (10.8)
Related serious AEs	17 (3.4)	1 (1.6)	1 (0.8)
AEs leading to discontinuation	18 (3.6)	2 (3.1)	1 (0.8)
AEs leading to interruption	51 (10.1)	4 (6.3)	10 (8.3)
AEs leading to death	1 (0.1)	0	0

Source: Table 2.6.7 p74 of the submission; Table 11-2 p74 Study 105 Week 192 and Extension Period CSR; Source: Table 2.6.10 p86 of the submission; Source: Table 2.6.11 p90 of the submission.
AE = adverse event; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; IA = interim analysis, SAE = serious adverse event.
Patients with multiple events within a category is counted multiple times in that category.

Benefits/harms

6.30 All of the studies in this submission were non-comparative. As such, it was not possible to present an assessment of benefits-to-harms for ELX/TEZ/IVA compared with the nominated comparators in the F/any population aged 2 to 5 years.

Clinical claim

6.31 The submission claimed ELX/TEZ/IVA was superior in terms of effectiveness and comparable in terms of safety when compared with the nominated comparators (LUM/IVA for F/F population, IVA in F/G population, BSC in F/MF, F/RF, F/R117H and F/not yet characterised population) in patients aged 2 to 5 years with CF with at least one mutation in the F508del gene. The evaluation considered this claim was not well supported in the submission due to the following reasons:

- The pivotal studies, Study 111 and Study 112, were single arm studies and therefore could not inform a comparison with LUM/IVA or BSC. In the context of lifetime treatment, the evidence to support the long-term benefit of ELX/TEZ/IVA was limited given the short duration of the trials (Study 111 = 24 weeks, Study 112 = 48 week results available).
- Study 105, Study 107 and Study 119 presented the long-term benefit and safety of ELX/TEZ/IVA in F/F or F/MF populations aged ≥ 12 years (Study 105), F/F or F/MF populations aged ≥ 6 years (Study 107) and F/MF populations aged ≥ 6 years

(Study 119). Overall, the results of the OLEs are mixed, with the studies reporting improvements in some outcomes and a decline in others when compared to the parent study. The clinical relevance of an improvement in some outcomes and a decline in other outcomes is difficult to interpret, noting the small number of patients with available data (Study 107) and the relatively good $ppFEV_1$ at baseline (> 85 percentage points) in the studies conducted in patients aged ≥ 6 years. Based on age, the patients in Study 105, 107 and 119 were not representative of the proposed target population. Therefore, the capacity to inform the long-term effectiveness in patients who commence ELX/TEZ/IVA treatment from 2 years of age was not supported.

- The above studies were conducted in patients with the F/MF or F/F genotypes and therefore the capacity to inform superior effectiveness and comparable safety compared to BSC in the F/RF, F/R117H, F/not yet characterised populations and compared to IVA in the F/G population was not supported.

6.32 The submission claimed that the efficacy of ELX/TEZ/IVA can be extrapolated to other mutations where there is currently no direct clinical evidence in the paediatric population. This claim relies on an assumption that the efficacy of the CFTR modulators is independent of the underlying genotype. The submission did not present translation studies or other evidence to support that assumption. The pre-PBAC response stated the therapeutic effects of ELX/TEZ/IVA in F/MF patients aged 2 to 5 years observed in Studies 111 and 112 indicate that a single F508del-CFTR mutation is sufficient to drive clinical benefit. Additionally, the pre-PBAC response stated that as the disease process in CF patients of all age groups stems from a common aetiology of dysfunctional CFTR protein that is targeted by ELX/TEZ/IVA, the outcome of treatment with ELX/TEZ/IVA is expected to be comparable between younger age groups and adults.

6.33 The PBAC has previously considered the magnitude of benefit of commencing ELX/TEX/IVA before 12 years of age was not able to be quantified with the available data; however, acknowledged that preventing decline in lung function from a younger age was likely to be beneficial (para 7.1, ELX/TEZ/IVA PSD, November 2022 PBAC Meeting with March 2023 Addendum). It is likely that the same uncertainly regarding the magnitude of benefit is likely to apply in the consideration of early treatment between the ages of 2 to 5 years.

6.34 The claim of non-inferior safety appeared to be adequately supported across the F/F and F/MF patient populations. The evidence provided by the submission suggested ELX/TEZ/IVA was generally well tolerated throughout the period of the trials presented. No critical safety concerns were raised by additional longer-term data in Study 105, Study 107 of Study 119. Elevated transaminases was a pre-defined adverse event of special interest (AESI) and was observed in all the studies. The PI recommends assessments of ALT and AST and total bilirubin are conducted prior to initiating

ELX/TEZ/IVA, every 3 months during the first year of treatment, and annually thereafter.

6.35 The PBAC noted the lack of clinical evidence for some populations but considered that, on balance, the claim of superior comparative effectiveness versus the nominated comparators was likely to be reasonable.

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

Economic analysis

6.37 The submission presented a base case modelled cost-utility analysis for the F/F (ELX/TEZ/IVA versus LUM/IVA) and F/MF (ELX/TEZ/IVA versus BSC) populations aged ≥2 years separately, as well as a combined analysis across those populations. No comparative economic evaluation was presented for the F/G, F/RF, and F/R117H populations. Instead, the submission presented a cost comparison of ELX/TEZ/IVA against current CFTR treatments to support the use of ELX/TEZ/IVA for these patient groups. The submission presented an analysis it termed Scenario 1 where only patients aged 2 to 5 years (the requested age for PBS listing) were included in the model and a Scenario 2 (in those aged ≥2 years) where the relative rate of decline (rROD) of $ppFEV_1$ was varied to 80% and 100% (base case of 90%). A summary of the key components of the economic evaluation is presented in Table 9.

Table 9: Summary of model structure, key inputs and rationale

Component	Description
Type of analysis	Cost-utility analysis
Outcomes	Costs; Quality-adjusted life-years
Time horizon	Lifetime; mean age for the combined populations (F/F and F/MF) at commencement of treatment of 20.3 years for the base case and 3.5 years for Scenario 1.
Method used to generate results	Individual patient microsimulation
Health states	Based on lung function: Normal ($ppFEV_1$ >90%), Mild ($ppFEV_1$ 70-90% predicted), Moderate ($ppFEV_1$ 40-70% predicted), Severe ($ppFEV_1$ <40% predicted)
Cycle length	First two years: 4-week cycle length From two years: 52-week cycle length
Transition probabilities/Efficacy	Treatment effects based on pivotal RCT evidence and ITCs (e.g. improved $ppFEV_1$; reduced PEx; improved weight-for-age z-scores; SwCl (Study 111; Study 106, Study 116, Study VX13-809-011, Study 102, Study 109) (Zemanick et al., 2021b, Vertex, 2021, Milla et al., 2017, Vertex, 2020, Ratjen et al., 2017b, Taylor-Cousar et al., 2017)
	Baseline $ppFEV_1$ decline based on large longitudinal registry analyses (de Boer et al., 2011, Konstan et al., 2007).
	Long-term reduction in the rate of $ppFEV_1$ decline (rROD): CFFPR, Study 102 (F/MF; 24-week study) and Study 103 (F/F; 4-week study), Study 105.
	Baseline hazard function for survival: Irish CF data registry
	Relationship between surrogate outcomes and survival: Liou 2001
Software	Microsoft Excel making use of Visual Basic.

Source: Table 3.1.1, p131 of the submission.

BSC = best supportive care; CF = cystic fibrosis; CFFPR = US CF Foundation Patient Registry; CFTR = cystic fibrosis transmembrane conductance regulator protein; F/F = F508del/F508del genotype; F/MF = F508del/minimal function genotype; IVA = ivacaftor; ITC = indirect comparison analysis; PEx = pulmonary exacerbations; ppFEV1 = percent predicted forced expiratory volume in one second; RCT = randomised controlled trial; rROD = relative rate of decline; SwCl = sweat chloride

6.38 Overall, the economic model was similar to that previously seen by the PBAC in other CFTR-modulator submissions including the LUM/IVA submission at the July 2023 PBAC meeting and the ELX/TEZ/IVA submission at the November 2022 PBAC meeting. The PBAC has previously raised issues about the structure, inputs and interpretation of the results of the economic model; issues that remain applicable to the current submission are summarised in Table 10.

Table 10: Key issues from previous ELX/TEZ/IVA and other CFTR (re)submissions remain applicable to the economic model presented in this submission.

Items	Issues	Potential effects	Source (para, PSD, month of the PBAC meeting)
Comparators	Less informative comparison: should have presented a comparison between early treatment (as proposed in the younger ages) versus late treatment (existing listing in the older age groups).	Likely overestimate of benefits of ELX/TEZ/IVA	6.42, ELX/TEZ/IVA, Nov 2022 6.29, LUM/IVA, Jul 2023
Surrogates to target clinical outcomes (Liou et al., 2001)	Inappropriateness of the assumption of causality and additivity in survival effects. Mismatch between the original design of the equation (absolute levels of risks) and its application in the submission (relative risks).	Favours ELX/TEZ/IVA	6.44, 6.50, LUM/IVA, Jul 2017. 6.51, LUM/IVA, Jul 2018
Baseline hazard of mortality in the Australian CF population (Irish data), and model validation for baseline survival	Unsuitability of historical Irish CF (survival) data for current Australian CF. Biased additional decline in $ppFEV_1$ to the baseline mortality of the Irish data in estimating BSC survival. Lower predicted median survival in BSC patients compared to the Irish cohort (survival result based on the Gompertz)	Overestimate of mortality for BSC, favouring ELX/TEZ/IVA.	6.48, 6.49 LUM/IVA, Jul 2018
Acute increase in $ppFEV_1$	Likely smaller acute increase in $ppFEV_1$ in younger patients than older patients.	Overestimate of benefits for ELX/TEZ/IVA.	6.56, ELX/TEZ/IVA, Nov 2022
Health utility	Exaggeration of health state differences in utility. Use of utility values higher than general population. Unsuitability of EQ-5D-5L tool for young populations. The overall approach taken to determine utilities (clinician proxy completion) remained inappropriate.	Overestimate of health outcomes for ELX/TEX/IVA.	6.47, ELX/TEZ/IVA, Mar 2021 6.31, LUM/IVA, Jul 2023
Loss of exclusivity (LoE)	Inappropriate application of price reductions due to LoE	Underestimate costs of ELX/TEZ/IVA	6.54, ELX/TEZ/IVA, Nov 2022
Compliance	Lower compliance rate in the economic model than the clinical studies.	Underestimate costs of ELX/TEZ/IVA	6.46, 6.47 ELX/TEZ/IVA, Mar 2021

Source: Developed as part of the Commentary

BSC = best supportive care; CF = cystic fibrosis; ELX = elexacaftor; EQ-5D-5L = EuroQoL five dimensions five levels; IVA = ivacaftor; Jul = July; Mar = March; Nov = November; LoE = loss of exclusivity; LUM = lumacaftor; PBAC = Pharmaceutical Benefits Advisory Committee; $ppFEV_1$ = percent predicted forced expiratory volume in one second; PSD = Public Document Summary; TEZ = tezacaftor

6.39 The base case economic analysis in the submission was for a population ≥2 years of age and therefore included the cost-effectiveness for those aged ≥6 years. The analysis was dominated by patients aged ≥6 years accounting for 87.6% of the modelled population. This was inappropriate given that those aged ≥6 years are already eligible for treatment. The ESC agreed with the evaluation that Scenario 1, which was restricted to the population aged 2 to 5 years, aligns better with the proposed listing and appears more informative in terms of the cost-effectiveness of the proposed PBS listing than the base case analysis.

6.40 The economic model relied on the application of efficacy data from 6 to 11 years, and those 12 years of age and older to the proposed population of 2 to 5 years, relying on data seen by the PBAC in the previous ELX/TEZ/IVA submissions (March 2021 and November 2022 PBAC meeting). The submission did not provide any translation studies to support the application of the treatment effect data from older populations to the proposed, younger age group.

6.41 The submission applied the baseline decline in $ppFEV_1$ rates in the BSC arm based on data from Konstan et al. (2007) and de Boer et al. (2011) which have been used previously in CFTR submissions. However, the rates of decline in $ppFEV_1$ from these studies were higher than those from other sources recently reviewed by the PBAC. For example, in patients aged ≥ 12 years, the rates were reported to be between -1.87% to -2.29% (based on the PBAC's review of the managed access plan for the supply of LUM/IVA and TEZ/IVA for the treatment of F/F; para 4.17, LUM/IVA PSD, PBAC July 2021 Meeting with December 2021 Addendum), compared with -2.47% in this economic model. Additionally, the submission presented data from Lee et al. (2023) based on an analysis matching F/F and F/MF patients receiving ELX/TEZ/IVA in Phase 3 clinical trials with patients in the US Cystic Fibrosis Foundation Patient Registry (mean age 25.77 years). The results from that analysis suggested a rate of decline in those receiving BSC of -1.92% (95% CI, -2.16 to -1.69 from the pooled analysis), lower than the -2.34% presented in Konstan et al. (2007) (mean age in 13 to 17 group is 15.2 years; Table 1, p136, Konstan et al., 2007). The ESC considered the Lee 2023 data is likely to represent a baseline decline in $ppFEV_1$ in BSC patients that is more reflective of modern treatment practice and should be used to inform the economic model. The ESC noted this increased the ICER in the Scenario 1 model from $155,000 to < $255,000 per QALY to $155,000 to < $255,000 per QALY. The pre-PBAC response noted the Konstan 2007 study is larger (Konstan N=4,866; Lee N=1,714) and included patients with a $ppFEV_1$ <40 where the Lee study did not. Further, the Lee BSC cohort is constrained by the clinical trial inclusion criteria to which it was matched, whereas Konstan is reflective of the natural history of the broader CF population and therefore better reflects the real-world distribution of CF patients. For these reasons, the pre-PBAC response stated the Konstan study provided a more appropriate estimate of the natural history of $ppFEV_1$ for Australian CF patients.

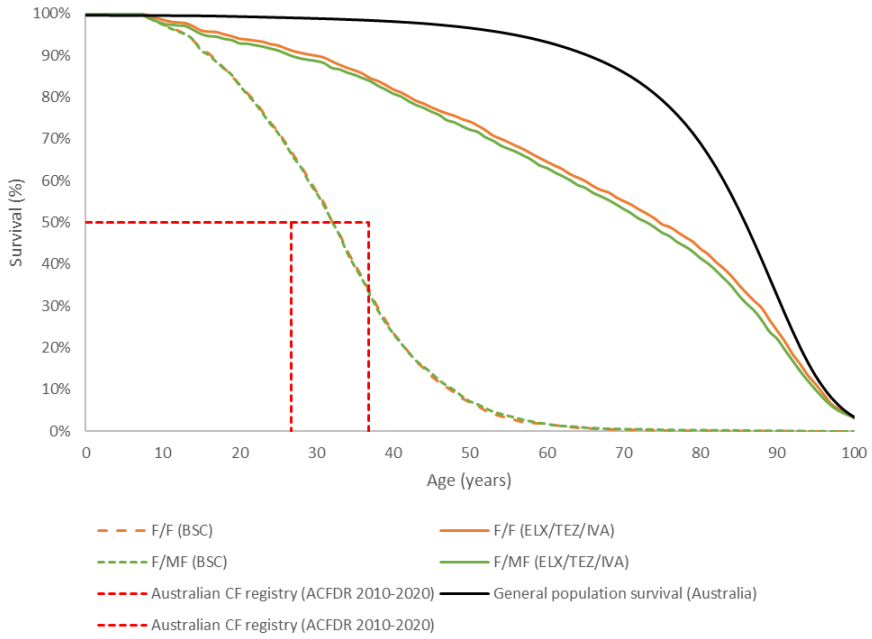
6.42 The submission assumed that the acute increase in $ppFEV_1$ in patients aged 2 to 5 years is the same as in those aged 6 to 11 years (13.9% for F/F and 11% for F/MF).

While it is reasonable to expect there will be an increase in $ppFEV_1$ following treatment, the magnitude of that increase among patients aged 2 to 5 may not be the same as that observed in the 6 to 11 years age group, largely because those aged 2 to 5 years have better lung function at baseline (therefore there is less capacity for improvement compared to those with worse baseline lung function). A similar concern was raised by the ESC in its consideration of ELX/TEZ/IVA for patients aged 6 to 11 years: "in the initial years of treatment the absolute increase in $ppFEV_1$ would likely be smaller in patients aged 6 to 11 years compared with those aged ≥12 years as the lung function in the young patients is, on average, higher" (para 6.56, ELX/TEZ/IVA PSD, PBAC meeting November 2022).

6.43 In the economic model, the submission applied a 90% rROD for the lifetime of patients receiving ELX/TEZ/IVA. In support of the use of such data the submission presented additional data (192 weeks) from Study 105 on the long-term follow-up of $ppFEV_1$ in F/F and F/MF patients aged ≥12 years, updating what was previously considered by the PBAC in November 2022 for the 6 to 11 year age group (at that time 144 weeks) (para 6.22, ELX/TEZ/IVA PSD, November 2022 PBAC meeting). The submission noted that the additional data shows the stabilisation of $ppFEV_1$ in the long-term and claimed that it equates to rROD of ≥100% compared to BSC and that the use of 90% is a conservative assumption. Overall, it remained unclear whether the efficacy data from the study in those aged ≥ 12 years is applicable to the proposed younger population aged 2 to 5 years and whether the assumed effect persists for a lifetime while receiving treatment.

6.44 Results for model validation presented by the submission in the form of a trace of predicted time to event outcomes (OS) based on Scenario 1, compared with data from the ACFDR 2010-2020, and the Australian general population are presented in Figure 1.

Figure 1: Model validation survival curves (All CUA) of 2-5 years patients (Scenario 1)



Source: Figure 3.1.8, p154 of the submission.
ACFDR = Australian Cystic Fibrosis Data Registry; BSC = best supportive care; CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator protein; CUA = cost-utility analysis; ELX = elexacaftor; F/F = F508del/F508del genotype; F/MF = F508del/minimal function genotype; IVA = ivacaftor; TEZ = tezacaftor
The model assumed 100% survival for patients during the ages of 2-5 years, as $ppFEV_1$ (the key parameter needed to estimate survival) is not tracked in the model until age of 6 years. The submission claimed that this is considered a reasonable assumption, as the Australian mortality rate for this age group is low.
The submission noted that the two red straight-dashed lines represent the median ages of death recorded for CF patients in Australia in 2010 and 2020, ranging between approximately 26.7 and 36.2 years obtained from the 2020 ACFDR (these median ages of death could not be verified during the evaluation).

6.45 The model predicted median age of death in F/F patients of 81.1 years and F/MF patients of 79.4 years and that approximately 20% of patients remained alive at 91 years. This predicted long-term survival appears to be optimistic and highly uncertain given it relied heavily on extrapolated data, specifically from Study 105. In its consideration of ELX/TEZ/IVA for patients aged 6 to 11 years, the PBAC noted that the estimated median survival (a median age of death of 77 and 74 years for F/F and F/MF patients, respectively) appeared to be optimistic and highly uncertain given it relied on heavily extrapolated data from a clinical study and that approximately 20% of patients remained alive at 91 years, which appeared optimistic given a similar proportion of the general Australian population would be expected to be alive at 91 years of age (para 6.48, ELX/TEZ/IVA PSD, November 2022 PBAC meeting). The same concerns are likely to apply for the estimates of survival for the 2 to 5 year old submission.

6.46 There are a number of unusual estimates that seem unrealistic in terms of $ppFEV_1$ outcomes including:

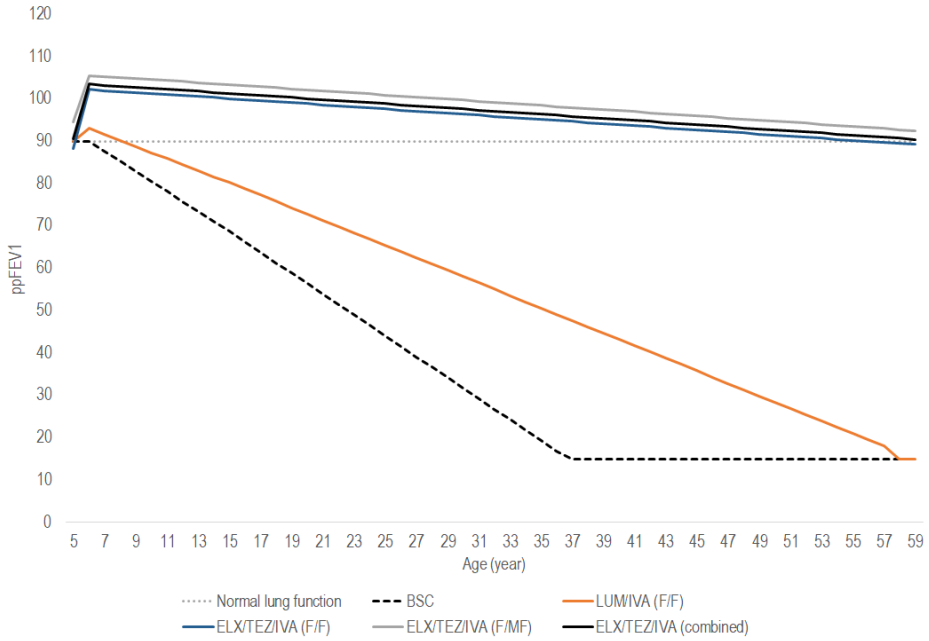
- The model predicted that mean change in ppFEV1 values for ELX/TEX/IVA would be slightly higher or unchanged compared to baseline after a lifetime time horizon

(mean change of +1.7% from a baseline of 69.5% in the base case and mean change of -0.4% from a baseline of 90.6% in Scenario 1 for the combined population; see Figure 2). In other words, ELX/TEZ/IVA patients would have ppFEV1 at the end of their time in the model similar to their baseline value.

- The predicted ppFEV1 for BSC seems overly pessimistic. In the base case analysis, the model predicts that 314 (16%) patients receiving BSC will have a ppFEV1 of 15% or less at the end of the model's period. Of these, 74 (4%) patients are projected to have a ppFEV1 of less than 0, which seems erroneous. Similar estimates are observed for those receiving ELX/TEZ/IVA, but with much lower numbers (9 patients for less than 15% and 5 patients for less than 0), and for the estimates derived in Scenario 1.

These results for ppFEV$_1$ outcomes do not appear to be clinically plausible and call into question the operational validity of the model. Overall, the results bias in favour of ELX/TEZ/IVA in underestimating outcomes for BSC relative to ELX/TEZ/IVA.

Figure 2: Predicted change in ppFEV$_1$ over the modelled time horizon for patients aged 2-5 years (Scenario 1)



Source: Developed for the Commentary based on ppFEV$_1$ data from the submission
BSC = best supportive care; F/F = CF patient homozygous for the F508del-CFTR mutation; F/MF = F508del/minimal function genotype; ELX/TEZ/IVA = elexacaftor; IVA = ivacaftor; ppFEV1 = percent predicted forced expiratory volume in one second; TEZ = tezacaftor
The submission assumed that an acute increase in ppFEV$_1$ occurs at age 6 years; The grey dash line was included as a reference line to reflect the threshold considered 'normal lung function' (ppFEV$_1$ of >90%).

6.47 A summary of the key drivers of the model is presented in Table 11.

Table 11: Key drivers of the model (performed based on Scenario 1: 2 to 5 years population)

Description	Method/Value	Impact Scenario 1: $[redacted][1]/QALY gained
LoE	Model assumed 90% price reduction after 13.69 years for ELX/TEZ/IVA, and 2.69 years for LUM/IVA	High, favours ELX/TEZ/IVA, removing LoE assumptions increased the ICER to $[redacted][2]/QALY
Acute increase in $ppFEV_1$	Acute increase in $ppFEV_1$ for ELX/TEZ/IVA of 13.9% in F/F patients and 11.0% for F/MF patients.	High, favours ELX/TEZ/IVA, reducing acute increase in $ppFEV_1$ by 50% (7.0% for F/F patients, 5.5% in F/MF patients) increased the ICER to $[redacted][2]/QALY
Utility	Value of utility of $ppFEV_1$ >90% was set to 0.98, higher than the Australian norm of 0.91 (para 6.48, ELX/TEZ/IVA PSD, PBAC March 2021 meeting)	High, favours ELX/TEZ/IVA, using a value of 0.91 increased the ICER to $[redacted][2]/QALY
rROD	Base case assumed rROD in $ppFEV_1$ of 90% for ELX/TEZ/IVA compared to 80% in the aged ≥12 years submission.	High, favours ELX/TEZ/IVA, using 80% rROD increased the ICER to $[redacted][2]/QALY

Source: Developed during the evaluation

ELX = elexacaftor; ICER = incremental cost-effectiveness ratio; IVA = ivacaftor; LoE = loss of exclusivity; LUM = lumacaftor; PBAC = Pharmaceutical Benefits Advisory Committee; ppFEV1 = percent predicted forced expiratory volume in one second; PSD = public summary document; QALYs = quality-adjusted life-years; rROD = relative rate of decline; TEZ = tezacaftor

The redacted values correspond to the following ranges:

[1] *$135,000 to < $155,000*

[2] *$155,000 to < $255,000*

6.48 The results for the base case analysis and Scenario 1 for the combined population are provided in Table 12. The ICER for ELX/TEZ/IVA for the combined population in the base case analysis (aged ≥ 6 years) was estimated at $115,000 to < $135,000 compared with $155,000 to < $255,000/quality-adjusted life years (QALY) gained in Scenario 1 (aged 2 to 5 years).

Table 12: Results of the economic evaluation for the combined population [a]

Base case (aged 2≥ years)	**ELX/TEZ/IVA**	**LUM/IVA (F/F), BSC (F/MF)**	**Incremental**
Life Years	16.99	11.85	5.15
QALYs	14.35	8.24	6.11
Total Costs	$[redacted]	$[redacted]	$[redacted]
ICER (cost per LYG)			**$**[redacted][1]
ICER (cost per QALY gained)			**$**[redacted][2]
Scenario 1 (aged 2-5 years)	**ELX/TEZ/IVA**	**LUM/IVA (F/F), BSC (F/MF)**	**Incremental**
Life Years	18.87	14.84	4.02
QALYs	18.03	12.58	5.45
Total Costs	$[redacted]	$[redacted]	$[redacted]
ICER (cost per LYG)			$[redacted][3]
ICER (cost per QALY gained)			**$**[redacted][3]

Source: Table 3.1.29, p156, Table 3.1.30 of the submission; worksheet 'Results' of the economic model

BSC = best supportive care; CUA = cost-utility analysis; ELX = elexacaftor; ICER = incremental cost-effectiveness ratio; IVA = ivacaftor; LUM = lumacaftor; QALYs =, quality-adjusted life-years; TEZ = tezacaftor

[a] Combined population weighted by 62% F/F and 38% F/MF

The redacted values correspond to the following ranges:

[1] *$135,000 to < $155,000*

[2] *$115,000 to < $135,000*

[3] *$155,000 to < $255,000*

6.49 The results from Scenario 1, which was restricted to the population aged 2 to 5 years appear to be more informative for the proposed listing than the base case analysis. Including the younger demographic, consistent with the requested listing presented in Scenario 1, provides a more accurate reflection of the treatment's long-term cost-effectiveness, (and reflects that the cost-effectiveness for such treatments is significantly influenced by discounting given the longer time frames over which costs and outcomes accumulate).

6.50 The estimated cost-effectiveness results are uncertain, for the same reasons as noted for previous ELX/TEZ/IVA submission for patients aged 6 to 11 years where the ESC considered it remained unclear what the appropriate cost per patient per year is for the additional treatment due to starting treatment at a younger age (i.e., 6 to 11 years from ≥ 12 years at that meeting; para 6.56, ELX/TEZ/IVA PSD, November 2022 PBAC meeting). The ESC also noted that in the initial years of treatment the absolute increase in $ppFEV_1$ would likely be smaller in younger patients (aged 6 to 11 years) compared with older ages (aged ≥12 years) as the lung function in young patients is, on average, higher (para 6.56, ELX/TEZ/IVA PSD, November 2022 PBAC meeting). Overall, the ESC previously considered the magnitude of benefit associated with earlier treatment is unknown and hence the appropriate cost per patient for the additional years of treatment is also largely unknown (para 6.56, ELX/TEZ/IVA PSD, November 2022 PBAC meeting).

6.51 Additionally, the request to price ELX/TEZ/IVA the same for younger patients as for older patients would require the PBAC to accept a higher ICER for listing this drug for the 2 to 5 years age group, than it has for the older ages. Reducing the rROD to 80% increased the ICER to $155,000 to < $255,000/QALY compared to $135,000 to < $155,000 / QALY accepted by the PBAC for older patients which applied an rROD of 80% (para 6.60 and 7.11, ELX/TEZ/IVA Minute, November 2022 PBAC meeting). The pre-PBAC response stated that, consistent with the precedents for IVA and LUM/IVA, patients aged 2-5 years when initiating ELX/TEZ/IVA should be afforded the same equity of access at the same price as patients initiating treatment at 6 years or older.

6.52 The results of key univariate/multivariate sensitivity analyses are summarised in Table 13. The analyses conducted during the evaluation were based on Scenario 1. The results are sensitive to time horizon, discounting, the age of the population in the model, LoE, rROD, baseline $ppFEV_1$, acute increase in $ppFEV_1$, baseline decline in $ppFEV_1$, and utility. The ESC noted that, incorporating a number of plausible changes to assumptions, the ICER may be as high as $255,000 to < $355,000 per QALY.

Table 13: Sensitivity analyses (combined population)

Analysis	Incremental cost	Incremental QALY	ICER	Changed from base case
Base case	**$[redacted]**	**6.11**	[redacted][1]	
Scenario 1 (aged 2 to 5 years)	$[redacted]	5.45	[redacted][2]	+[redacted]%
Scenario 2: rROD of ppFEV$_1$: 100% (base case: 90%)	$[redacted]	6.74	[redacted][1]	-[redacted]%
Scenario 2: rROD of ppFEV$_1$: 80% (base case: 90%)	$[redacted]	5.39	[redacted][3]	+[redacted]%
LoE removed (base case 90% reduction after 13.69 years for ELX/TEZ/IVA, and 2.69 years for LUM/IVA)	$[redacted]	6.11	[redacted][2]	+[redacted]%
Sensitivity analyses conducted during the evaluation (based on Scenario 1: 2 to 5 years)				**Changed from base case [b]**
Time horizon of 20 years (base case: lifetime)	$[redacted]	1.36	[redacted][4]	+[redacted]% (+[redacted]%)
Discount rate – costs and benefits 0% (base case: 5%)	$[redacted]	39.56	[redacted][5]	-[redacted]% (-[redacted]%)
Discount rate – costs and benefits 3.5% (base case: 5%)	$[redacted]	8.96	[redacted][6]	-[redacted]%, (-[redacted]%)
LoE removed (base case: 90% price reduction after 13.69 years for ELX/TEZ/IVA, and 2.69 years for LUM/IVA)	$[redacted]	5.45	[redacted][2]	+[redacted]% (+[redacted]%)
Higher baseline ppFEV$_1$ [c]	$[redacted]	5.28	[redacted][2]	+[redacted]% (+[redacted]%)
Lower acute increase in ppFEV$_1$ of ELX/TEZ/IVA [a]	$[redacted]	4.68	[redacted][2]	+[redacted]% (+[redacted]%)
No acute increase in ppFEV$_1$ of ELX/TEZ/IVA [d]	$[redacted]	4.04	[redacted][2]	+[redacted]% (+[redacted]%)
Lower baseline rates of lung decline of -1.92% per year applied for aged ≥9 years based on Lee et al., 2023 (base case: between -2.39 to -2.47%)	$[redacted]	4.92	[redacted][2]	+[redacted]% (+[redacted]%)
Utility of ppFEV$_1$ >90% of 0.91[e] (base case: 0.98)	$[redacted]	4.80	[redacted][2]	+[redacted]% (+[redacted]%)
rROD of ppFEV$_1$: 100% (base case: 90%)	$[redacted]	5.83	[redacted][3]	+[redacted]% (-[redacted]%)
rROD of ppFEV$_1$: 80% [f] (base case: 90%)	$[redacted]	4.90	[redacted][2]	+[redacted]% (+[redacted]%)
Multivariate analyses				
Higher baseline ppFEV$_1$ and lower acute increase in ppFEV$_1$ of ELX/TEZ/IVA	$[redacted]	4.62	[redacted][2]	+[redacted]% (+[redacted]%)
Lower acute increase in ppFEV$_1$ of ELX/TEZ/IVA, and 100% rROD of ppFEV$_1$	$[redacted]	5.15	[redacted][2]	+[redacted]% (+[redacted]%)
LoE removed, lower acute increase in ppFEV$_1$ of ELX/TEZ/IVA, lower baseline rates of lung decline of -1.92% per year applied for aged ≥9 years, Lower utility of ppFEV$_1$ >90% lung function of 0.91	$[redacted]	3.70	[redacted][7]	+[redacted]% (+[redacted]%)

Source: Table 3.1.32, pp159-160 of the submission; developed as part of the Commentary.

BSC = best supportive care; CFTR = Cystic fibrosis transmembrane conductance regulator protein; CUA = cost-utility analysis; ELX = elexacaftor; F/F = F508del/F508del genotype; F/MF = F508del/minimal function genotype; ICER = incremental cost-effectiveness ratio; pulmonary exacerbation; IVA = ivacaftor; LoE = loss of exclusivity; LUM = lumacaftor; QALYs =, quality-adjusted life-years; ppFEV1 = percent predicted forced expiratory volume in one second; rROD = relative rate of decline; TEZ = tezacaftor

[a] reducing acute increase in ppFEV$_1$ by 50%.

[b] percentages in parentheses are change based on the Scenario 1.

[c] arbitrability assuming baseline ppFEV$_1$ of no lower than 80% based on the 2021 ACFDR report (base case: not applied).

[d] assuming increase in ppFEV$_1$ for ELX/TEZ/IVA of 3% (equivalent to LUM/IVA) for F/F and 0% for F/MF.

[e] based on a utility of the Australian norm (para 6.48, ELX/TEZ/IVA PSD, PBAC March 2021 meeting).

[f] as in a revised base case in the pre-PBAC response for 6 to 11 years submission (para 6.60, ELX/TEZ/IVA PSD, November 2022 PBAC meeting).

The redacted values correspond to the following ranges:

[1] *$115,000 to < $135,000*

[2] *$155,000 to < $255,000*

[3] *$135,000 to < $155,000*

[4] *$555,000 to < $655,000*

[5] *$45,000 to < $55,000*

[6] *$95,000 to < $115,000*

[7] *$255,000 to < $355,000*

6.53 The proposed price of ELX/TEZ/IVA for the F/RF and F/R117H population was the same as the price for LUM/IVA as currently listed for patients aged ≥ 2 years. For F/G patients, the submission proposed the same effective price of ELX/TEZ/IVA used for F/F and F/MF in the economic model. For the F/G population, the submission argued that given that the current annual cost of treating F/G patients, listing ELX/TEZ/IVA will result in cost-savings (as IVA is most costly than ELX/TEZ/IVA).

6.54 The calculation of the proposed effective price is presented in Table 14. The requested annual effective price of ELX/TEZ/IVA for the proposed listing was calculated as $, the same as the annual effective price for the 6 to 11 years patient population.

Table 14: Prices by subpopulations informing effective price

Genotype grouping	Effective price in this 2 to 5 years submission (100% compliance)
F/F	$
F/MF (incl. 80% FNYC)	$
F/G	$[a]
F/RF (incl. 20% FNYC)	$
F/R117H	$
Effective weighted price across populations	**$**

Table 2.7.2, p110 of the submission.
CF = Cystic Fibrosis; ELX = elexacaftor; F/F = F508del/F508del genotype; F/MF = F508del/minimal function genotype; F/G = F508del/gating mutation; FNYC = F not yet characterised; F/RF = F508del/residual function mutation; F/RF = F508del/R117H mutation; Rounding applies.
[a] Set to the same weighted effective price as ELX/TEZ/IVA in F/F and F/MF populations initiating therapy aged ≥6 years.
The submission did not explicitly state the weightings applied across the genotype groups. However, they appear to be similar to those applied in the 6 to 11 years submission (para 6.58, ELX/TEZ/IVA PSD, November 2022 PBAC meeting).

Drug cost/patient/year

6.55 A summary of the cost per patient per year is presented in Table 15. The price per pack for ELX/TEZ/IVA in the economic model was the specific price for the F/F and F/MF subpopulations ($), whereas the price per pack used in the financial estimates was the weighted price across all subpopulations ($).

Table 15: Drug cost per patient for proposed and comparator drugs

	ELX/TEZ/IVA		LUM/IVA (F/F only)	
	Model (F/F and F/MF population)	Financial estimates (F/any population)	Model	Financial estimates
Price per pack/ 28-day supply (A)	$	$	$	
Compliance (B)	90.00%	95.00%	90%	84.33%
Cost/patient/year ((365.25/28)pack/year*A*B))	$	$	$	$

Source: Developed for the Commentary
ELX = elexacaftor; F/F = F508del/F508del genotype; F/MF = F508del/minimal function genotype; IVA = ivacaftor; LUM = lumacaftor; TEZ = tezacaftor

Estimated PBS usage & financial implications

6.56 This submission was not considered by DUSC.

6.57 The submission presented an epidemiological approach to the financial estimates of ELX/TEZ/IVA in F/any patients aged 2 to 5 years who have at least one F508del mutation in the CFTR gene. The approach used in developing the estimates was similar

to that presented to the PBAC at the November 2022 meeting for the PBS listing of ELX/TEZ/IVA in the ≥6 years population. Eligible populations were estimated separately according to three groups: those eligible for use under the existing Deeds including F/F and F/G patients; those ineligible for use under the existing Deeds including F/MF, F/RF, and F/R117H patients; and those eligible for use under the existing Deeds but not currently on treatment i.e., CFTR naïve F/F patients and grandfathering patients. A summary of the data sources and parameter values applied in the financial estimates is presented in Table 16.

Table 16: Key inputs for financial estimates

Parameter	Source	Estimate
Patients included within the subsidisation caps under existing Deeds		
F/F		
Prevalence population in Yr1 (n)	ACFDR (2022 data)	147
LUM/IVA patients	Assumption (informed by 6-11 years submission)	67%
Switch to ELX/TEZ/IVA	Assumption	100%
F/G		
Prevalence population in Yr1 (n)	ACFDR (2022 data)	13
IVA patients	Assumption (informed by 6-11 years submission)	100%
Switch to ELX/TEZ/IVA	Assumption	100%
Patients not currently eligible for PBS-reimbursed CFTR modulators		
Prevalent population (F/MF; F/RF, F/R117H) in Yr1 (n)	ACFDR (2022 data). Assumption: 80% of F/not yet characterised is assumed to have F/MF, and 20% to have F/RF	87; 31; 13
Annual uptake rate (F/MF; F/RF, F/R117H)	Clinical opinion and uptake in other comparable markets.	98%; 80%; 80%
F/F patients not captured in the Deed calculations		
F/F patients (n)	ACFDR (2022 data) and the sponsor's databases	49 [a]
Annual uptake rate	Local clinical opinion and uptake in other markets	98%
Discontinuation at Yr1 and Yr2	Study 102 and 109 for Yr1, Study 105 for Yr2	1.4% (Yr1) and 4.2% (Yr2)
Compliance (full year treatment with 100 compliance = 13.04 scripts)		
ELX/TEZ/IVA	Internal Australian market data of patients aged 6–11 years on existing CFTR modulators, and of ELX/TEZ/IVA compliance in global markets.	95%
LUM/IVA	Based on the 6-11 years and ≥12 years submission	84.33%
IVA		80.60%

Source: Table 4.1.1, p163; Table 4.1.2, p164; Table 4.1.3; p165; Table 4.1.4, p166; Table 4.3.1; p169; Table 4.3.3, p170; Table 4.3.5, p171; Table 4.3.7, p173; Table 4.4.2, p175; Table 4.5.1, p177; Table 4.5.3, p179; Table 4.6.5, p181; Table 4.6.7 of the submission.

ACFDR = Australian Cystic Fibrosis Data Registry; CFTR = Cystic fibrosis transmembrane conductance regulator; ELX = elexacaftor; F/G = CF patient heterozygous for the F508del in the CFTR gene with a gating mutation; F/F = homozygous for F508del-CFTR mutations; F/MF = heterozygous for F508del-CFTR mutation with a second minimal function allele; F/R117H = CF patients who are heterozygous for F508del in the CFTR gene with a R117H mutation; F/RF = heterozygous for F508del-CFTR with a second residual function mutation; IVA = ivacaftor; LUM = lumacaftor/ivacaftor; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; PSD = public document summary; TEZ = tezacaftor; Yr = Year

[a] 1 compassionate access, 4 in clinical trials, and 44 additional patients (described in this Commentary as CFTR naïve).

6.58 The submission used the same inputs, including uptake/switching rates, discontinuation, and compliance, as accepted for the 6 to 11 years submission.

6.59 The submission used a recent year of data from ACFDR (2022) as a source of epidemiological data to estimate the number of patients in each subpopulation. During the evaluation, the DUSC Secretariat provided the use of LUM/IVA and IVA in patients aged 2 to 5 years. A comparison of the submission's estimate for F/F and F/G

patients based on 2022 ACFDR versus the DUSC Secretariat data is presented in Table 17.

Table 17: Comparison of F/F and F/G patients between the estimate in the submission and DUSC Secretariat data

F/F				F/G	
Submission (2022 ACFDR) (Year 1)			DUSC Secretariat prevalent LUM/IVA aged 2 to 5 years patients (2019 to 2023)	Submission (2022 ACFDR) (Year 1)	DUSC Secretariat prevalent IVA aged 2 to 5 years patients
Total	LUM/IVA	CFTR Naïve			
147[a]	99	44	14 (2019), 134 (2020), 149 (2021), 148 (2022), 132 (2023) [b]	13	24 (2017), 24 (2018), 22 (2019), 17 (2022), 21 (2021), 24 (2022), 20 (2023) [b]

Source: Table 4.3.9, p174 of the submission; Analysis provided by the DUSC during the evaluation (D1546- Lumcaftor+Ivacaftor and Ivacaftor for cystic fibrosis).

[a] 5 grandfathering (4 in clinical trial, 1 in compassionate programme)

[b] January to September

6.60 The submission estimated the total prevalent F/F population to be 147 (Year 1). Based on the previous use of LUM/IVA in 6 to 11 year olds, the submission assumed that 67% of the prevalent population, or 99 patients in Year 1 will receive LUM/IVA under the current Deed (if there is no ELX/TEZ/IVA listing) and there will be 33% of the prevalent F/F population (48-49 patients depending on rounding) who are untreated (44 patients) or are treated outside the Deed (5) and that become eligible for ELX/TEZ/IVA. However, DUSC Secretariat data for the use of LUM/IVA in patients aged 2-5 years during 2019 to 2023 show that there were 134 (2020) to 148 (2022) LUM/IVA treated F/F patients. Therefore, the evaluation considered the number of LUM/IVA patients estimated by the submission (99 patients) is likely underestimated relative to current use (148). The PSCR noted the most recent published ACFDR Report (2021) stated that as of December 2021, there were 94 of 125 patients aged 2-5 being treated with LUM/IVA (Table 4.8, 2021 ACFDR Report), with 108 patients on LUM/IVA at any time throughout the year. The PSCR noted this aligned with the submission estimate of 99 patients in 2024. The ESC noted the number of patients estimated in the PBS data (provided by the DUSC Secretariat) is a count of patients receiving at least one script in the year which may overestimate the point prevalence. The evaluation noted the estimated number of F/G patients aged 2 to 5 years receiving IVA of 13-14 per year is lower than the data provided by the DUSC at on average of 22 per year during 2018 – 2022 and 24 patients in 2022. The PSCR noted the DUSC Secretariat data for IVA would also capture non-F gating patients which are not relevant to ELX/TEZ/IVA.

6.61 As with the previous ELX/TEZ/IVA aged 6 to 11 years submission, this submission assumed that patients receive treatment for the whole of the first year of listing as well as applying a high uptake rate in the first year, including switching from existing PBS-CFTR listed drugs to ELX/TEZ/IVA. The evaluation considered this might not be reasonable. The PSCR stated CF clinics have become extremely efficient in initiating new patients on CFTRm therapy and noted that upon listing of ELX/TEZ/IVA for CF patients aged 12 years and older, approximately 2,000 patients were initiated on treatment within 5 months of listing. The PSCR stated an even faster uptake has been

seen in relation to the uptake of ELX/TEZ/IVA in the population aged 6-11 years (which is the same prescriber group that will be initiating ELX/TEZ/IVA for 2–5-year-olds).

6.62 A summary of the estimated use and financial implications is presented in Table 18.

Table 18: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications of ELX/TEZ/IVA						
Cost to PBS/RPBS less copayments	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Estimated financial implications for LUM/IVA, IVA						
Cost to PBS/RPBS less copayments	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Net financial implications						
Net cost to PBS/RPBS	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]
Net cost to MBS	[redacted][6]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]
Net cost to PBS/RPBS/MBS	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]
Net cost to PBS/RPBS by subpopulations						
F/F	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]
F/G [c]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
F/MF	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][6]
F/RF	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]
F/R117H	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]

Source: Table 4.3.9, p174; Table 4.4.3, p175; Table 4.5.4, p179; Table 4.6.8, p184; Source: Table 4.7.2, p186 of the submission. Developed during the evaluation using the financial worksheet model.

ELX = elexacaftor; F/F = homozygous for F508del-CFTR mutations; F/MF = heterozygous for F508del-CFTR mutation with a second minimal function allele; F/R117H = CF patients who are heterozygous for F508del in the CFTR gene with a R117H mutation; F/RF = heterozygous for F508del-CFTR with a second residual function mutation; IVA = ivacaftor; LUM = lumacaftor; MBS= Medicare Benefit Schedule; PBS=Pharmaceutical Benefit Scheme; RPBS = Repatriation Schedule of Pharmaceutical Benefits; TEZ = tezacaftor

[a] Assumption about the CFTR naïve F/F patients and estimated IVA (F/G) patients based on DUSC data

[b] Arbitrarily reduces initiating treatment patients by 30%.

[C] Noting that the negative estimate for F/G is due to the cost per year of IVA being higher than ELX/TEZ/IVA.

The redacted values correspond to the following ranges:

[1] *< 500*

[2] *500 to < 5,000*

[3] *$30 million to < $40 million*

[4] *Net cost saving*

[5] *$20 million to < $30 million*

[6] *$10 million to < $20 million*

[7] *$0 to < $10 million*

6.63 The total cost to the PBS/RPBS of listing ELX/TEZ/IVA was estimated to be $20 million to < $30 million in Year 6, and a total of $100 million to < $200 million in the first 6 years of listing. The evaluation considered the estimated net financial implications for the PBS/RPBS are likely overestimated due to the underestimated cost offset as well as the overestimate for the use of ELX/TEZ/IVA in the first year of listing previously discussed.

6.64 The ESC noted there is some overlap between the patient population in this submission and the population recommended for IVA in November 2023 (i.e., F/R117H, F/RF and F/other population aged 2 to 6 years) that should be accounted for in the financial estimates.

Quality Use of Medicines

6.65 The submission did not present a discussion of quality use of medicine issues. However, the administration of ELX/TEZ/IVA granules mixed with food may present a wastage risk in very young children (potentially through regurgitation of the ELX/TEZ/IVA mixed with food, or refusal to eat, and drug stability of only one hour when mixed) (para 2.3, LUM/IVA PSD, July 2019 PBAC meeting).

Financial Management – Risk Sharing Arrangements

6.66 The submission stated that the extension to the listing of ELX/TEZ/IVA in the 2 to 5 years population will necessitate an increase to the current subsidisation cap levels set out in the multi-product Deed of Agreement for PBS listed ELX/TEZ/IVA, LUM/IVA and TEZ/IVA indications, in line with the financial estimates presented herein. At its November 2023 meeting, the PBAC advised that the net cost of the extended IVA population should be included in the existing RSA for ivacaftor with the financial caps increased to include the cost of the additional patient population and considered a combined RSA for the CFTR modulators, as proposed by the sponsor, was reasonable (para 7.9, IVA PSD, November 2023 PBAC meeting).

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

7 PBAC Outcome

7.1 The PBAC recommended that the restriction for elexacaftor/ tezacaftor/ ivacaftor (ELX/TEZ/IVA) be extended to include the treatment of cystic fibrosis (CF) in patients who are aged 2 to 5 years and who have at least one F508del mutation on the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The PBAC also recommended that two granule formulations should be made available under Section 100 (Highly Specialised Drugs Program) to facilitate dosing in children aged 2 to < 6 years. The PBAC noted the evidence presented could not accurately quantify the benefit of treating patients with ELX/TEZ/IVA from a younger age but acknowledged treatment from a young age was likely to be beneficial. The PBAC considered ELX/TEZ/IVA was likely to be cost-effective for this population at the same unit price as the current PBS listing (for patients over 6 years of age). The PBAC noted the financial estimates would need to be reduced to account for patients eligible for treatment with ivacaftor (IVA) (as recommended at the November 2023 PBAC meeting).

7.2 The PBAC noted the strong consumer support for extending the availability of ELX/TEZ/IVA to CF patients aged 2 to 5 years.

7.3 The PBAC noted the submission nominated lumacaftor/ ivacaftor (LUM/IVA) as comparator in the F/F population, IVA monotherapy as comparator in the F/G population and best supportive care (BSC) as comparator in the F/MF, F/RF and F/R117H populations. The PBAC considered the nominated comparators were reasonable; however, it would have been informative to compare commencing

treatment with ELX/TEZ/IVA between the ages of 2 to 5 years with commencing treatment with ELX/TEZ/IVA at 6 years of age or older in each of these populations.

7.4 The PBAC was satisfied that ELX/TEZ/IVA provides, for some patients, an improvement in efficacy over the nominated comparators.

7.5 The PBAC advised the proposed restriction criteria was appropriate with the population criterion "Patient must be 2 years of age or older" amended to "Patient must be 2 to 5 years of age" as discussed in paragraph 3.3

7.6 The PBAC noted that the submission presented one single arm trial in patients 2 to 5 years of age evaluating the safety and efficacy of ELX/TEZ/IVA granules in patients with F/F and F/MF genotypes (Study 111, 24 weeks) and an extension study (Study 112, 48 weeks). The PBAC noted that treatment with ELX/TEZ/IVA resulted in an improvement from baseline to week 24 in outcomes of sweat chloride, lung clearance index and growth parameters. The PBAC noted percent predicted forced expiratory volume in one second ($ppFEV_1$) was not collected in the studies due to the difficulty in conducting spirometry measures in young children.

7.7 The PBAC noted the submission did not present any clinical evidence for the F/RF, F/G or F/R117H populations for any age group. However, consistent with its consideration in patients aged 6 to 11 years, the PBAC considered the results in studies in patients ≥ 12 years of age supported the likely benefit of ELX/TEZ/IVA in the younger age group.

7.8 The PBAC considered the magnitude of benefit of commencing ELX/TEX/IVA before 6 years of age was not able to be quantified with the available data; however, acknowledged that preventing decline in lung function from a younger age was likely to be beneficial.

7.9 The PBAC considered the claim that ELX/TEZ/IVA is of comparable safety to the nominated comparators in the 2 to 5 years population was reasonable.

7.10 The PBAC noted the incremental cost effectiveness ratio (ICER) for the combined F/F and F/MF population was $155,000 to < $255,000 per quality adjusted life year (QALY) gained. The PBAC noted the economic model was similar to that previously seen by the PBAC for ELX/TEZ/IVA and other CFTR modulators, and reiterated the issues previously raised about the structure, inputs and interpretation of results of the economic model. Notwithstanding the high and uncertain ICER, the PBAC considered it plausible that ELX/TEZ/IVA would be cost-effective in this population at a unit price no higher than that for the ≥ 6 years population.

7.11 The PBAC considered that, on balance, the methodology for estimating the number of patients aged 2 to 5 years treated with ELX/TEZ/IVA was reasonable.

7.12 The PBAC advised that the extended population should be included in the existing Risk Sharing Arrangement for ELX/TEZ/IVA, LUM/IVA and TEZ/IVA (and IVA should the November 2023 recommendation be implemented). The PBAC advised the net cost of listing ELX/TEZ/IVA for patients aged 2 to 5 years could be added to the expenditure

caps currently in place. The PBAC considered the net cost of listing ELX/TEZ/IVA should take into account the reduced utilisation of IVA in the F/RF and F/R117H population which was recommended in November 2023.

7.13 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 ELX/TEZ/IVA:

a) Based on the available evidence the magnitude of benefit of starting treatment from a younger age was not able to be quantified and therefore the criteria of having a substantial and clinically relevant improvement in efficacy compared to starting at an older age was not met;

b) The treatment is expected to address a high and urgent unmet clinical need for the F/MF, F/RF and F/R117H populations as they currently have no PBS-listed alternative treatment options (until they are at least 6 years of age);

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

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

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
ELEXACAFTOR+TEZACAFTOR+IVACAFTOR (&) IVACAFTOR					
Elexacaftor 100 mg + tezacaftor 50 mg + ivacaftor 75 mg granules [28] (&) ivacaftor 75mg granules [28], 56 sachets	NEW MP	1	1	5	Trikafta
Elexacaftor 80 mg + tezacaftor 40 mg + ivacaftor 60 mg granules [28] (&) ivacaftor 59.5 mg granules [28], 56 sachets	NEW MP	1	1	5	Trikafta
Restriction Summary [new] / Treatment of Concept: [new]					
Category / Program: Section 100 – Highly Specialised Drugs Program					
Prescriber type: ☒Medical Practitioners					
Restriction type: ☒ Authority Required (in writing only via post/HPOS upload)					
Edit Restriction Summary 12961 / ToC: 12972: Authority Required					
Concept ID	**Category / Program:** Section 100 – Highly Specialised Drugs Program [Public and Private Hospitals]				
	Prescriber type: ☒Medical Practitioners				

	Restriction type: ☒Authority Required – non-immediate/delayed assessment by Services Australia
	Condition: Cystic fibrosis
	Indication: Cystic fibrosis
	Treatment Phase: Initial treatment
	PR level administrative advice
	Administration advice: No increase in the maximum quantity or number of units may be authorised.
	Administration advice: No increase in the maximum number of repeats may be authorised
	Administration advice: Special Pricing Arrangements apply.
	Administrative Advice: For the purposes of this restriction, PBS-subsidised 'CFTR modulator' means ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor and elexacaftor/ tezacaftor/ ivacaftor.
	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
	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
	AND
	Clinical criteria:
	Patient must have at least one F508del mutation in the cystic fibrosis transmembrane conductance (CFTR) gene
	AND
	Clinical criteria:
	The treatment must be given concomitantly with standard therapy for this condition
	AND
	Clinical Criteria:
	Patient must have either chronic sinopulmonary disease or gastrointestinal and nutritional abnormalities, prior to initiating treatment with this drug
	Population criteria:
	Patient must be 2 to 5 years of age
	Prescribing instructions: This pharmaceutical benefit is not PBS-subsidised for this condition in a patient who is currently receiving one of the strong CYP3A4 inducers outlined in the Product Information.

	Prescribing instructions: The authority application must be in writing and must include: (1) a completed authority prescription; and (2) a completed Cystic Fibrosis Authority Application Supporting Information Form; and (3) details of the pathology report substantiating the patient having at least one F508del mutation - 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

Edit Restriction Summary 12942 / ToC: 12962: Authority Required	
	Treatment Phase: 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
	AND
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	The treatment must be given concomitantly with standard therapy for this condition.
	AND
	Population criteria:
	Patient must be 2 to 5 years of age
	Prescribing instructions: This pharmaceutical benefit is not PBS-subsidised for this condition in a patient who is currently receiving one of the strong CYP3A4 inducers outlined in the Product Information.
	The authority application must be in writing and must include: (1) a completed authority prescription form; and (2) a completed Cystic Fibrosis elexacaftor, tezacaftor with ivacaftor 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 PBAC's continued recognition of the importance of early treatment with this positive recommendation to extend the listing of Trikafta® (elexacaftor with tezacaftor and with ivacaftor, and ivacaftor) to include patients aged 2 through to 5 years who have at least one F580del mutation in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene (F/any population). Vertex is working with the Department of Health and Aged Care to ensure access for these children as soon as possible.