7.01 ELEXACAFTOR/TEZACAFTOR/IVACAFTOR
Elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg film-coated tablets co-packaged with ivacaftor 150 mg film-coated tablets, TRIKAFTA™, Vertex Pharmaceuticals (Australia) Pty Ltd.

1 Purpose

1.1 The early re-entry resubmission sought listing of elexacaftor/ tezacaftor/ ivacaftor (ELX/TEZ/IVA) for the treatment of cystic fibrosis (CF) patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. This has previously been referred to as the 'F/any' population.

2 Background

Registration status

2.1 ELX/TEZ/IVA was TGA registered on the 24 March 2021 for the treatment of CF in patients aged 12 years and older who have at least one F508del mutation in the CFTR gene.

Previous PBAC consideration

2.2 The PBAC has previously considered ELX/TEZ/IVA at the March 2021, May 2021 and July 2021 PBAC meetings. The PBAC Public Summary Documents (PSDs) for the March 2021 consideration include addendums for the May 2021 and July 2021 considerations.

2.3 In March 2021, the PBAC considered a request to list ELX/TEZ/IVA for the F/any population which included: (1) patients who are homozygous for the F508del-CFTR mutation (F/F population); (2) patients who are heterozygous for F508del in the CFTR gene with a residual function mutation (F/RF population); (3) patients who are heterozygous for F508del in the CFTR gene with a gating mutation (F/G population); (4) patients who are heterozygous for F508del in the CFTR gene with a minimal function mutation (F/MF population) and (5) patients who are heterozygous for F508del in the CFTR gene with a second mutation that is unknown or not yet characterised as gating, residual function or minimal function (F/not yet characterised).

2.4 In May 2021, an additional population was identified that was previously included as part of the F/not yet characterised population: patients who are heterozygous for

F508del in the CFTR gene with an R117H mutation (F/R117H population). Additionally, the PBAC considered it was reasonable to reallocate 80% of the F/not yet characterised population in the Australian Cystic Fibrosis Data Registry (ACFDR) to the F/MF population and 20% to the F/RF population.

2.5 In July 2021, the PBAC recommended the listing of ELX/TEZ/IVA for the F/MF population only.

3 Requested listing

3.1 The sponsor provided amended prescribing instructions (shown in red text) to the restriction proposed previously. The Secretariat's suggested additions are included in italics, and suggested deletions are included in strikethrough.

MEDICINAL PRODUCT medicinal product pack	Max. qty packs	Max. qty units	№.of Rpts	DPMQ	Proprietary name and manufacturer
ELEXACAFTOR + TEZACAFTOR+IVACAFTOR (&) IVACAFTOR					
Elexacaftor 100mg + tezacaftor 50mg + ivacaftor 75mg [56] (&) ivacaftor 150mg [28], 84	1	1	5	$21,375 (published)	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 – non-immediate/delayed assessment by Services Australia					
Condition: cystic fibrosis - at least one F508del mutation in the cystic fibrosis transmembrane conductance (CFTR) gene					
Indication: cystic fibrosis - at least one F508del mutation in the cystic fibrosis transmembrane conductance (CFTR) gene					
Treatment Phase: Initial 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					
Population criteria:					
Patients must be 12 years of age or older.					
Prescribing Instructions					
The patient must be registered in the Australian Cystic Fibrosis Database Registry.					
~~Treatment must not be given to a patient who has an acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease in the last 4 weeks prior to commencing this drug.~~					
Trikafta is not PBS-subsidised for this condition in a patient who is currently receiving a strong CYP3A4 inducer as outlined in the Product Information.					

For the purposes of this restriction, PBS-subsidised 'CFTR modulator' means ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor and elexacaftor/ tezacaftor/ ivacaftor. 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) ~~a copy of the pathology report detailing the molecular testing for the patient having at least one F508del mutation~~; ~~and~~ the result of a FEV_1 measurement performed within a month prior to the date of application. Note: FEV_1 must be measured in or under the supervision of a cystic fibrosis clinic. If the patient has an acute infective exacerbation, then the best FEV_1 measurement in the six months prior to treatment initiation should be documented; and (4) current CYP3A4 inhibitors, CYP3A4 inducers and IV antibiotics; and (5) height and weight measurements at the time of application; and (*6)details of the name of the molecular testing for the patient having at least one F508del mutation including: (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* ~~(7) a baseline measurement of the number of days of CF-related hospitalisation (including hospital-in-the home) in the previous 12 months.~~ For patients who have initiated non-PBS-subsidised treatment prior to [Insert listing date], date of initiating treatment, baseline FEV_1 and hospitalisation dates prior to initiating treatment (where available) should be provided.
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
Administration Advice
No increase in the maximum quantity or number of units may be authorised.
No increase in the maximum number of repeats may be authorised
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:
Clinical criteria:
The treatment must be given concomitantly with standard therapy for this condition.
AND

Population criteria:
Patients must be 12 years of age or older.
Prescribing Instructions
~~Treatment must not be given to a patient who has an acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease in the last 4 weeks prior to commencing this drug.~~ ~~Patients who have an acute infective exacerbation at the time of assessment for continuing therapy may receive an additional one month's supply in order to enable the assessment to be repeated following resolution of the exacerbation.~~
For the purposes of this restriction, PBS-subsidised 'CFTR modulator' means ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor and elexacaftor/ tezacaftor/ ivacaftor. 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) the result of a FEV_1 measurement performed within a month prior to the date of application. Note: FEV_1 must be measured in or under the supervision of a cystic fibrosis clinic. If the patient has an acute infective exacerbation, then the best FEV_1 measurement in the six months prior to treatment initiation should be documented; and (4) current CYP3A4 inhibitors, CYP3A4 inducers and IV antibiotics; and (5) height and weight measurements at the time of application; and ~~(6) a baseline measurement of the number of days of CF-related hospitalisation (including hospital in the home) in the previous 12 months.~~
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
Administration Advice
No increase in the maximum quantity or number of units may be authorised.
No increase in the maximum number of repeats may be authorised

3.2 The resubmission stated there were 206 patients receiving ELX/TEZ/IVA via the compassionate access program and 96 Australian patients receiving treatment in clinical trials that will be grandfathered to PBS-reimbursed supply.

3.3 The resubmission proposed amended wording for the collection of data and removal of the requirement to submit data concerning the number of days of CF-related hospital admissions. The pre-PBAC response stated that in response to the COVID-19 pandemic, patients treated with PBS- listed CFTRm were largely managed through TeleHealth, including measurement of their lung function utilising guided home spirometry. The pre-PBAC response stated that measurement of $ppFEV_1$ as proposed in the restriction, will afford more flexibility for clinics and patients while maintaining the quality of the data for PBS Authority Applications and ACFDR data entry. Further, the current requirement for absence of exacerbations perversely prevents the patients most likely to benefit from accessing ELX/TEZ/IVA treatment; baseline and continuing data requirements can be addressed by providing the best $ppFEV_1$ measurement in the previous six months.

3.4 The resubmission proposed removing the prescribing advice for co-administration of both CYP450 3A4 inducers and inhibitors that is currently included in the PBS listings for other CF modulators. This is on the basis that there is information concerning the interactions between ELX/TEZ/IVA and inducers/ inhibitors in the TGA approved product information. However, the Secretariat noted current PBS listings for CF modulators do not permit PBS subsidised treatment when co-administered with a CYP450 inducer. The Secretariat has proposed the addition of the prescriber instruction: Trikafta is not PBS-subsidised for this condition in a patient who is currently receiving a strong CYP3A4 inducer as outlined in the Product Information.

3.5 In line with online PBS authorities transformation principles, the Secretariat proposed an amendment of the requirement to submit a copy of the pathology to instead state the provision of: (i) name of pathology report provider, (ii) date of pathology report, (iii) unique identifying number/code that links the pathology result to the individual patient. The pre-PBAC response stated the sponsor supported this amendment only if it does not allow 'leakage' into populations without at least one F508del mutation (i.e., there must be a mechanism in place for Services Australia to confirm that the patient has at least one F508del mutation per the approved TGA indication) and provided it does not require information that is not uniformly reported by all pathology providers (i.e., use of unique patient identifier other than Medicare number).

4 Consideration of the evidence

Clinical trials

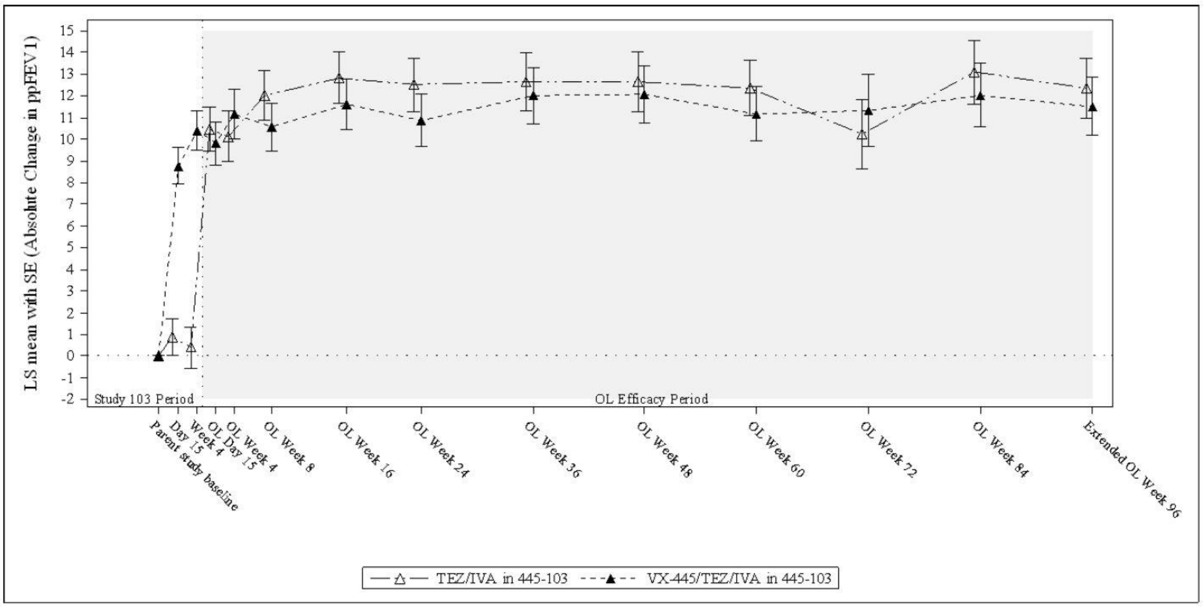
4.1 The March 2021 submission provided a second interim analysis (data cut-off 31 October 2019) from Study 105 which presented data from a total follow-up of 40 weeks for the F/F population and 48 weeks for F/MF population.

4.2 The resubmission presented results from a third interim analysis (IA3) of Study 105 (data cut-off 25 March 2021) with a total follow-up of 100 weeks for the F/F population and 120 weeks for the F/MF population.

4.3 The resubmission presented the results of a number of outcomes including absolute change from baseline in $ppFEV_1$, absolute change from baseline in sweat chloride, number of pulmonary exacerbations (PEx), time to first PEx, absolute change in body mass index (BMI) and absolute change from baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain score. The pre-PBAC response reiterated that improvements in the parent studies were sustained or increased for sweat chloride, BMI and CFQ-R Respiratory Domain score throughout an additional 96 weeks of treatment in Study 105.

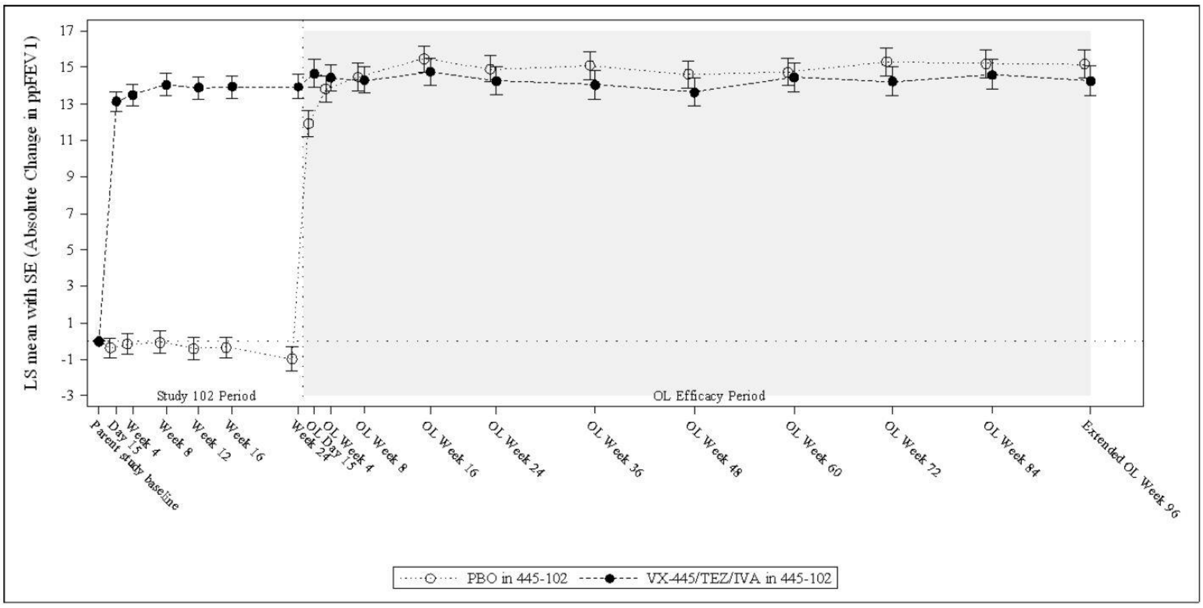
4.4 The absolute change from baseline in $ppFEV_1$ for Study 105 (IA3) is presented in Figure 1 for the F/F population and in Figure 2 for the F/MF population.

Figure 1: Study 105 (IA3 results): Absolute change from baseline in $ppFEV_1$ by Visit in F/F patients (Study 103/OL-FAS Study 105)



Abbreviations: , Full Analysis Set; F/F, CF patient homozygous for the *F508del-CFTR* mutation; IA3, interim analysis 3; IVA, ivacaftor; LS, least squares; MMRM, mixed-effects model for repeated measures; OL, open-label; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; SE, standard error; TEZ, tezacaftor;
Note: The y-axis corresponds to the LS means from the MMRM models at the Week 96 analysis.
Source: Study 105 Week 96 Analysis Summary, Figure 6-5 p.20

Figure 2: Study 105 (IA3 results): Absolute change from Baseline in ppFEV1 by Visit in F/MF patients (Study 102/OL-FAS Study 105)



Abbreviations: IA3, interim analysis 3; FAS, Full Analysis Set; F/MF, CF patient heterozygous for the *F508del* in the *CFTR* gene with a minimal function mutation; IVA, ivacaftor; LS, least squares; MMRM, mixed-effects model for repeated measures; OL, open-label; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; SE, standard error; TEZ, tezacaftor;
Source: Study 105 Week 96 Analysis Figure 6-1 p 15
Note: The y-axis corresponds to the LS means from the MMRM models at the Week 96 analysis.

4.5 The resubmission stated the results of the IA3 analysis for Study 105 confirm the robustness and durability of the benefits of ELX/TEZ/IVA treatment for up to a total of 120 weeks in F/MF patients and up to a total of 100 weeks in F/F patients supporting the long-term benefits of ELX/TEZ/IVA in patients with at least one F508del-CFTR mutation.

Cost per patient

4.6 A summary of the annual cost per patient (assuming 90% compliance) for the F/any population requested by the sponsor across the 4 submission is provided in Table 1.

Table 1: Cost per patient for the F/any population

	March 2021	May 2021	July 2021	December 2021
Annual cost per patient (assuming 90% compliance)	Requested by sponsor: $[redacted] (in pre-PBAC response) Proposed by PBAC: $[redacted] for the first 24 weeks of listing $[redacted] for a further 2 years of listing $[redacted] for supply beyond 2.5 years	Requested by sponsor: $[redacted] for the first year of listing (with a MAP to determine price subsequently) Proposed by PBAC: $[redacted] for the first year of listing $[redacted] for a further 2 years of listing $[redacted] for supply beyond 3 years	Proposal by sponsor: $[redacted] for first two years of listing (with a MAP to determine price subsequently) Recommended by PBAC: $[redacted] for the F/MF population with no MAP	Requested by sponsor: $[redacted]

Abbreviations: F/any, heterozygous for F508del-CFTR mutation; F/MF, heterozygous for F508del-CFTR mutation with a second minimal function allele; MAP, managed access program
Source: March 2021; PSD, paragraph 6.62, paragraph 7.73; May 2021: PSD, paragraph 9.3, paragraph 10.8; July 2021: sponsor proposal (Table 4), PSD, paragraph 12.8; December 2021: resubmission (Table 3.2.1).

4.7 The resubmission requested an effective price of $[redacted] per pack of ELX/TEZ/IVA which resulted in an annual cost per patient of $[redacted] (assuming 90% compliance). The calculation of the weighted price is presented in Table 2.

Table 2: Calculation of weighted annual effective prices

Population	% weight	Annual effective price at 90% compliance for each population	Weighted annual effective price at 90% compliance
F/F	53.23%	$[redacted]	$[redacted] annual price $[redacted] pack price
F/MF	27.51%	$[redacted]	
F/G	7.49%	$[redacted] [a]	
F/RF & F/R117H	11.77%	$[redacted]	
Total	100.00%		

Abbreviations: F/F, homozygous for *F508del-CFTR* mutations; F/G, heterozygous for F508del-CFTR mutation with a second gating mutation; F/MF, heterozygous for *F508del-CFTR* mutation with a second minimal function allele; F/RF, heterozygous for the *F508del-CFTR* mutation with a second residual function mutation; F/R117H, heterozygous for the *F508del-CFTR* mutation with a second R117H mutation;
[a] weighted price for F/F and F/MF applied to the F/G population
Note: F/F, F/MF and F/G prices calculated at 90% compliance; TEZ/IVA price 11 packs/year. Weighted annual pack price calculated from weighted annual price and 90% compliance. Rounding applies to all calculations.

4.8 The resubmission presented updated data from the ACFDR with revised population splits to inform the weighted price; however, stated "To ensure comparability of this resubmission with the previous considerations by the PBAC, the use of the 2019 ACDR data is retained in this resubmission. Vertex considers that, if required, the most efficient time point to make a change to the epidemiological data relied on for the financial and utilisation estimates will be at the time of post-PBAC procedures".

Economic analysis

4.9 During its March 2021 consideration of ELX/TEZ/IVA for the F/F and F/MF populations, the PBAC considered the following revisions to the submission's base case economic model were reasonable: (i) no treatment specific utility (ii) relative rate of decline in $ppFEV_1$ for ELX/TEZ/IVA of 42% (as previously accepted for lumacaftor/ ivacaftor (LUM/IVA)) and (iii) no increase in the cost of tezacaftor/ ivacaftor (TEZ/IVA) compared with that agreed previously for LUM/IVA. The PBAC also noted the incremental cost effectiveness ratio (ICER) applying a relative rate of decline in $ppFEV_1$ for ELX/TEZ/IVA of 61.5% as proposed in the submission.

4.10 The resubmission presented an economic model consistent with the PBAC's March 2021 consideration (as outlined in the paragraph above) with the exception of the relative rate of decline in $ppFEV_1$ for ELX/TEZ/IVA. The resubmission increased the relative rate of decline from that assumed in the March 2021 submission (61.5%) to 80%. The justification provided in the resubmission for the increase was the $ppFEV_1$ data available for Study 105 over the longer follow up period (as presented above).

4.11 The resubmission stated it had reweighted the F/F and F/MF populations in the economic model to account for reallocation of the F/not yet characterised population (weights of 65.92% and 34.08%, respectively).

4.12 The ICERs for the F/F population, the F/MF population and weighted across these two populations is presented in Table 3. The ICERs presented in Table 3 use a weighted annual effective price of $[redacted] (based on 90% compliance) for both populations.

Table 3: ICERs for F/F population, F/MF population and weighted across the two populations

Description	CUA vs TEZ/IVA in F/F population	CUA vs placebo in F/MF population	Combined (weighted)
Resubmission			
% Population	65.92%	34.08%	100%
Annual effective price at 90% compliance	$[redacted]		-
ICER with 80% rROD	[redacted][1]	[redacted][1]	[redacted][1]
ICER with 61.5% rROD	[redacted][1]	[redacted][1]	[redacted][1]
Impact of ELX/TEZ/IVA price on ICER			
ICER with 80% rROD + no price reduction for Trikafta due to patent expiry (annual effective price with 90% compliance $[redacted])	[redacted][2]	[redacted][1]	$[redacted][2]

Abbreviations: CUA, cost utility analysis; ELX/TEZ/IVA, elexacaftor/tezacaftor/ivacaftor; F/F, homozygous for F508del-CFTR mutations F/MF, heterozygous for F508del-CFTR mutation with a second minimal function allele; ICER, incremental cost effectiveness ratio; rROD, relative rate of decline; TEZ/IVA, tezacaftor/ ivacaftor

Source: Table 3.1.4 in resubmission;_TRI Aus CEM vs 3.1 Sept 2021.xls; paragraph 6.62 of PSD

The redacted values correspond to the following ranges:

[1]$155,000 to < $255,000

[2]$255,000 to < $355,000

4.13 A summary of the life years gained (undiscounted) and incremental costs and outcomes (discounted) generated by the economic model provided with the resubmission for each population at the requested cost per patient (assuming 90% compliance) is presented in Table 4.

Table 4: Summary of incremental costs and outcomes for base case presented in resubmission

	Incremental life years (undiscounted)	Incremental cost ($) (discounted)	Incremental effect (QALYs) (discounted)	ICER (cost/ QALY)
F/F population: ELX/TEZ/ IVA vs TEZ/IVA **Annual cost per patient:** $[redacted]	20.56	$[redacted]	4.74	[redacted][1]
F/MF population: ELX/TEZ/IVA vs BSC **Annual cost per patient:** $[redacted]	26.79	$[redacted]	6.72	[redacted][1]

Abbreviations: BSC best supportive care; ELX/TEZ/IVA, elexacaftor/tezacaftor/ivacaftor; F/F homozygous for F508del-CFTR mutations F/MF heterozygous for F508del-CFTR mutation with a second minimal function allele; ICER incremental cost effectiveness ratio; QALY quality adjusted life year; TEZ/IVA, tezacaftor/ ivacaftor

Source: TRI Aus CEM vs 3.1 Sept 2021.xls

The redacted values correspond to the following process:

[1]$155,000 to < $255,000

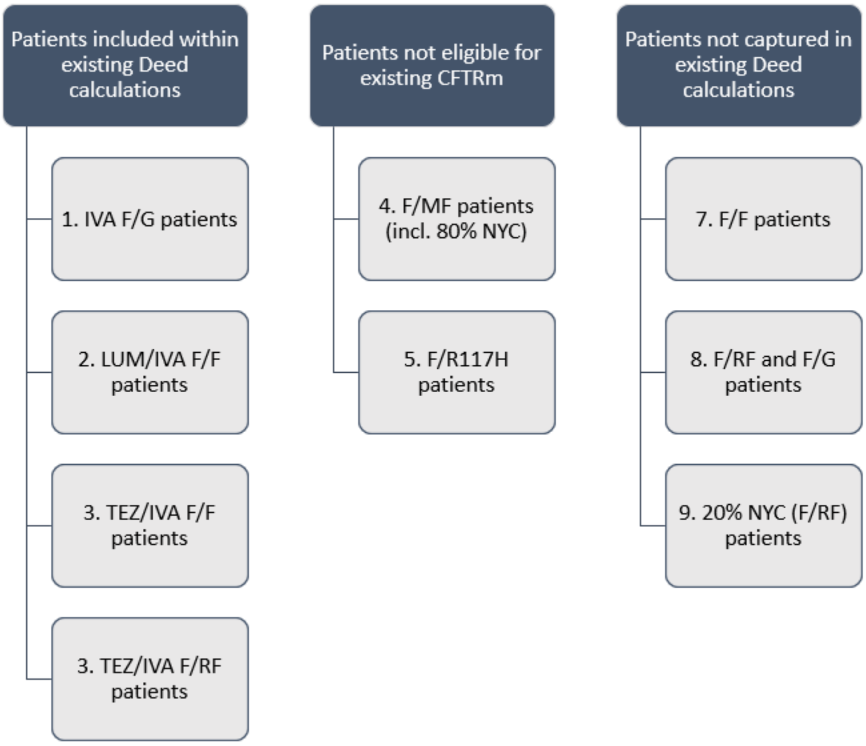
Estimated PBS utilisation and financial implications

4.14 The resubmission did not present estimates based on the PBAC's previous advice.

4.15 Instead, the resubmission proposed patient estimates that were largely unchanged from previous submission in that the treated population was based on ACFDR data, and inconsistent with previous PBAC advice that for the populations for which there was a PBS-listed CFTR-modulator available, previously agreed patient numbers for these listings would be appropriate to inform the estimated utilisation.

4.16 The resubmission identified 9 populations in estimating the total eligible ELX/TEZ/IVA population, as summarised in Figure 3.

Figure 3: Proposed eligible patient populations for ELX/TEZ/IVA



Abbreviations: CFTRm, cystic fibrosis transmembrane conductance regulator modulator; ELX, elexacaftor; F/F, homozygous for F508del-CFTR mutations; F/G, heterozygous for F508del-CFTR mutation with a second gating mutation; F/MF, heterozygous for F508del-CFTR mutation with a second minimal function allele; F/RF, heterozygous for the F508del-CFTR mutation with a second residual function mutation; F/R117H, heterozygous for the F508del-CFTR mutation with a second R117H mutation IVA, ivacaftor; LUM, lumacaftor; NYC, not yet characterised; TEZ, tezacaftor
Source: Figure 4.2.1 of the resubmission

4.17 The approach remained similar to the May 2021 proposal, however the resubmission made adjustments to uptake rates to the some of the populations and proposed alternate discontinuation rates for the treatment naïve populations.

4.18 In March 2021, and again in May 2021, the PBAC advised that estimates for the F/F, F/RF and F/G groups should be based on previously agreed estimates for the listing of the available CFTR modulators on the PBS. The PBAC has previously considered it may be reasonable for the eligible patients from those populations that are currently ineligible for PBS-listed CFTR modulator therapy (i.e. F/MF and F/R117H groups), to be estimated using an epidemiological approach with reference to the ACFDR current patient numbers.

4.19 As per its previous May 2021 proposal, the resubmission maintained that there are F/F, F/RF, F/G and 20% of patients not yet characterised (who would later be characterised as F/RF), who are not captured within the existing Deed calculations. The additional patients were estimated using ACFDR data, participation in Vertex compassionate access scheme and clinical trials.

4.20 The resubmission states at time of listing, the estimates for LUM/IVA were split into a 6-11 years and a 12+ cohort, and that incident patients were not included in the 12+ model for simplicity. Including the incident patients from the 6-11 year estimates of the F/F population would be appropriate.

4.21 The resubmission claims that the Department's methodology to estimate the F/F and F/RF patient numbers incorrectly reapplies uptake or discontinuation rates. This is not accurate. The Department estimates following the March 2021 and May 2021 meetings, based on the PBAC advice, did not apply discontinuation rates to the estimated numbers. Applying uptake rates was appropriate as the original LUM/IVA estimates did not apply any rates of uptake (i.e. assumed 100% uptake of full time equivalent (FTE) patients).

4.22 *Discontinuation rates:* The PBAC has previously advised that applying the same discontinuation rates as applied to LUM/IVA at time of listing would be appropriate. The resubmission proposed alternate discontinuation rates for ELX/TEZ/IVA of 1.4% in Year 1 (based on pooled rate from Study 109 and Study 103 over 24 weeks) and 4.2% in Year 2 (based on Study 105 over 96 weeks). This is higher than previously proposed by the sponsor, but still lower than the LUM/IVA rates previously advised (6.8% at Year 1 and 14.9% at Year 2). The pre-PBAC response claimed that there is a marked difference in the benefit/risk profile of LUM/IVA and ELX/TEZ/IVA, and that fewer adverse events have been observed with ELX/TEZ/IVA compared with LUM/IVA.

4.23 *Uptake rates:* the main adjustments to the uptake rates from the May 2021 proposal were a reduction in the switching rate for eligible F/G patients currently treated with IVA; and increase in uptake in Years 4 to 6 for treatment naïve F/RF not yet characterised patients.

4.24 In May 2021, PBAC accepted the proposed eligible patients and uptake rates as requested for the F/MF and F/R117H populations.

4.25 In March 2021, PBAC advised uptake rates of:

- 75% increasing to 85% in the F/F population; and
- 50% each year for the F/RF and F/G populations.

4.26 The net cost of the listing to the PBS/RPBS in the resubmission was estimated to be \$700 million to < \$800 million over 6 years. A summary of the number of FTE patients expected to be treated with ELX/TEZ/IVA for Population 1 to Population 9 was provided in the resubmission.

Table 5: Financial implications of listing ELX/TEZ/IVA on the PBS

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Resubmission						
Total FTE patients receiving ELX/TEZ/IVA	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total number of ELX/TEZ/IVA packs dispensed	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Cost to PBS	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Changed listing	-[redacted][4]	-[redacted][5]	-[redacted][5]	-[redacted][5]	-[redacted][5]	-[redacted][6]
Net cost to PBS	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]
March 2021 pre-PBAC response						
Total FTE patients receiving ELX/TEZ/IVA	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Cost to PBS	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Changed listing	-[redacted][6]	-[redacted][6]	-[redacted][6]	-[redacted][6]	-[redacted][6]	-[redacted][6]
Net cost to PBS	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]
May 2021 proposal						
Total FTE patients receiving ELX/TEZ/IVA	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Cost to PBS	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Changed listing	-[redacted][5]	-[redacted][5]	-[redacted][5]	-[redacted][6]	-[redacted][6]	-[redacted][6]
Net cost to PBS	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]
Department estimates based on May 2021 PBAC advice						
Total FTE patients receiving ELX/TEZ/IVA	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Cost to PBS	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]
Changed listing	-[redacted][7]	-[redacted][8]	-[redacted][8]	-[redacted][8]	-[redacted][8]	-[redacted][8]
Net cost to PBS*	[redacted][7]	[redacted][9]	[redacted][9]	[redacted][10]	[redacted][10]	[redacted][10]

* Cost per patient decreased over time (refer to paragraph 10.8 of PSD)
Abbreviations: ELX/TEZ/IVA, elexacaftor/ tezacaftor/ ivacaftor; FTE, full-time equivalent.
Source: Compiled by Secretariat, Table 4.3.1 & 4.4.1 sponsor submission, UCM-Release-3-Workbook-v108_TRIKAFTA, “3c. Impact – proposed (eff)”
The redacted values correspond to the following ranges:
[1]500 to < 5,000
[2]20,000 to < 30,000
[3]$200 million to < $300 million
[4]$80 million to < $90 million
[5]$90 million to < $100 million

[6]$100 million to < $200 million
[7]$60 million to < $70 million
[8]$70 million to < $80 million
[9]$50 million to < $60 million
[10]$30 million to < $40 million

4.27 Offsets are reduced in the resubmission compared to the May 2021 proposal, due to the lower proposed estimate of F/G patients switching from IVA (which is currently more expensive than the proposed price of ELX/TEZ/IVA).

4.28 The estimated utilisation and financial impact of the July 2021 PBAC recommendation for listing in the F/MF population, at a net cost of $300 million to < $400 million over 6 years, are outlined below.

Table 6: Financial implications of listing ELX/TEZ/IVA on the PBS for the F/MF population, as recommended by PBAC at the July 2021 meeting

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Department estimates based on PBAC July 2021 advice						
Total FTE patients receiving ELX/TEZ/IVA	[redacted][1]	[redacted][2]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total number of ELX/TEZ/IVA packs dispensed	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Net cost to PBS	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]

Abbreviations: ELX/TEZ/IVA, elexacaftor/ tezacaftor/ ivacaftor; F/MF heterozygous for F508del-CFTR mutation with a second minimal function allele
Source: Compiled by Secretariat
The redacted values correspond to the following ranges:
[1]< 500
[2]500 to < 5,000
[3]5,000 to < 10,000
[4]$50 million to < $60 million

Financial Management – Risk Sharing Arrangements

4.29 In its July 2021 recommendation for listing of ELX/TEZ/IVA for the F/MF population, the PBAC advised that a 100% reimbursement over subsidisation caps based at the level of the financial estimates should apply.

4.30 The resubmission argued that the RSA caps for ELX/TEZ/IVA should be reflective of the total eligible patients, and reiterated that a Special Pricing Arrangement with a unit level rebate was being proposed, therefore the cost-effective price per patient was not dependent on the financial caps being met (as is the case for the LUM/IVA and TEZ/IVA).

5 PBAC outcome

5.1 The PBAC recommended the listing of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) for the treatment of cystic fibrosis (CF) patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (the F/any population).

5.2 The PBAC noted that the resubmission was not consistent with the Committee's advice in March 2021 and May 2021 in relation to the F/any population with regard to the cost-effective price and the patient estimates. However, in making its recommendation, the PBAC noted that there was a high clinical need for ELX/TEZ/IVA especially for those patient populations that are not eligible for a currently PBS-subsidised CFTR modulator therapy. The PBAC considered that ELX/TEZ/IVA could be brought within an acceptable incremental cost effectiveness ratio (ICER) range with a price reduction, and in the context of accepting the resubmission's proposed patient estimates as reflecting the upper end of the range of likely use.

5.3 The PBAC recalled that in July 2021, it had recommended the listing of ELX/TEZ/IVA for the F/MF population in order to facilitate access to ELX/TEZ/IVA for a patient population that does not currently have access to treatment. However, the sponsor had chosen not to progress listing based on this recommendation.

5.4 The PBAC recalled the strong consumer support for making ELX/TEZ/IVA available for CF patients as soon as possible.

F/RF and F/R117H populations

5.5 The PBAC noted the proposed effective annual price for the F/RF and F/R117H populations ($[redacted] assuming 90% compliance) was consistent with its previous recommendations (March 2021 for F/RF and May 2021 for F/R117H). The PBAC noted that a submission regarding the LUM/IVA Managed Access Program was being considered at the same meeting, and considered that the LUM/IVA and TEZ/IVA cost-effective price determined following that advice should be the basis of the cost-minimised price of ELX/TEZ/IVA in the F/RF population, and flow-on to the F/R117H population. The PBAC considered the equi-effective doses were elexacaftor 200 mg once daily/ tezacaftor 100 mg once daily/ ivacaftor 150 mg every 12 hours and tezacaftor 100 mg once daily/ ivacaftor 150 mg every 12 hours.

F/F, F/MF and F/G populations

5.6 The PBAC noted for the remaining populations (F/F, F/MF and F/G) that the proposed weighted annual price ($[redacted] assuming 90% compliance) was higher than requested in previous submissions.

5.7 The PBAC noted the resubmission presented results from a third interim analysis (IA3) of Study 105 (data cut-off 25 March 2021) with a total follow-up of 100 weeks for the F/F population and 120 weeks for the F/MF population. The PBAC noted these data supported that treatment with ELX/TEZ/IVA resulted in maintenance of $ppFEV_1$ over the period of follow-up.

5.8 In the economic model, $ppFEV_1$ was used to predict clinical outcomes such as pulmonary exacerbations, lung transplantations, quality of life and survival. Without treatment, $ppFEV_1$ was estimated to decline by approximately 2.5 percentage points per year over the patient's lifetime for both the F/MF and F/F populations. Treatment with ELX/TEZ/IVA was assumed to reduce this decline in $ppFEV_1$ to approximately 0.5

percentage points per year, i.e. the rate of decline in $ppFEV_1$ was reduced by 80% with treatment (rROD = 80%). The PBAC acknowledged that, for the period over which data are available (100-120 weeks), rROD = 80% is a reasonable estimate. While the pre-PBAC response claimed that the application of 80% rROD in the economic model is conservative, the PBAC considered that there remained considerable uncertainty around the long-term benefits of treatment and as to whether a rROD = 80% would be sustained over a patient's lifetime.

5.9 The PBAC noted a key driver of the ICER was the cost of ELX/TEZ/IVA and that its cost was reduced by 90% after 16.35 years to account for potential generic competition. The PBAC has previously considered the application of such price reductions to be inappropriate and contrary to the PBAC Guidelines. The PBAC further considered that experience with CFTR modulator treatments indicates that it is highly unlikely that this price reduction would be realised, in part due to future patients being treated with alternative newer therapies.

5.10 **F/MF:** The PBAC noted for the F/MF population that the modelled difference in $ppFEV_1$ for patients treated with ELX/TEZ/IVA versus best supportive care (BSC) resulted in an 87% reduction in the annual rate of pulmonary exacerbations, 4.4% fewer patients undergoing a lung transplantation and an increase in average life expectancy from 14 years to 40 years. The PBAC considered the modelled additional benefits with ELX/TEZ/IVA to be uncertain and likely optimistic, at least in part due to underestimating the outcomes achieved with BSC, assuming a low rate of decline in $ppFEV_1$ over the patient's entire life time, and the exclusion of patients with severe ($ppFEV_1$<40%) and normal ($ppFEV_1$>90%) lung function.

5.11 Based on the weighted price proposed in the resubmission (annual effective price with 90% compliance of $[redacted], Table 2) together with a 90% price reduction after 16.35 years, and the modelled outcomes as per paragraph 5.10, the ICER was estimated in the submission to be $155,000 to < $255,000 per quality adjusted life year (QALY) gained. The PBAC noted this ICER increased to $155,000 to < $255,000/QALY when the assumed 90% price reduction was removed for ELX/TEZ/IVA, and to $155,000 to < $255,000/QALY if the extent of benefit modelled over the longer term was reduced by using a rROD of 61.5%. The PBAC considered these ICERs to be very high, and the ICER for the submission's scenario to be uncertain given the extent of benefit model and the inappropriate incorporation of the 90% price reduction. The PBAC recalled that an annual price of $[redacted] (with 90% compliance) was recommended for the F/MF population at its July 2021 meeting based on the high unmet need in this smaller population, and noted with this price the ICER reduced from $155,000 to < $255,000 to $115,000 to < $135,000/QALY. The PBAC noted the ICER increased to $155,000 to < $255,000/QALY with the inappropriate 90% price reduction removed and to $155,000 to < $255,000/QALY with the extent of benefit reduced (rROD of 61.5%). The PBAC considered the ICERs based on the price recommended at the July 2021 meeting to be high but acceptable for the

F/MF population given the high and currently unmet clinical need for treatment for these patients.

5.12 **F/F:** In the F/F economic model, the comparator treatment, TEZ/IVA, was assumed to reduce the rate of decline in $ppFEV_1$ to approximately 1.5 percentage points per year (rROD of 42% vs BSC). This compares to an approximate 0.5 percentage point decline with ELX/TEZ/IVA (paragraph 5.8). For the F/F population the modelled difference in $ppFEV_1$ for patients treated with ELX/TEZ/IVA versus TEZ/IVA resulted in a 73% reduction in the annual rate of pulmonary exacerbations, 4.1% fewer patients undergoing a lung transplantation and an increase in average life expectancy from 20 years to 41 years. As for the F/MF population, the PBAC considered the modelled additional benefits with ELX/TEZ/IVA to be uncertain and likely optimistic. The PBAC considered the total per patient cost of ELX/TEZ/IVA over the time horizon of the model was underestimated due to the applied 90% price reduction after 16.35 years.

5.13 Based on the weighted price proposed in the resubmission (annual effective price with 90% compliance of $[redacted], Table 2) together with a 90% price reduction after 16.35 years, and the modelled outcomes as per paragraph 5.12, the ICER was estimated in the submission to be $155,000 to < $255,000/QALY. The PBAC noted this ICER increased to $255,000 to < $355,000/QALY when the assumed 90% price reduction was removed for ELX/TEZ/IVA, and to $155,000 to < $255,000/QALY if the extent of benefit modelled over the longer term was reduced by using a rROD of 61.5%. The PBAC considered these ICERs to be unacceptably high, and the ICER for the submission's scenario to be underestimated given the extent of benefit modelled and the inappropriate incorporation of the 90% price reduction. The PBAC considered a price reduction of 25-30% would be required for this population to ensure reasonable confidence that an acceptable ICER would be achieved. The PBAC noted this would result in an ICER of $75,000 to < $95,000-$95,000 to < $115,000 /QALY for the resubmission's scenario, $155,000 to < $255,000-$155,000 to < $255,000/QALY with the 90% price reduction removed and $115,000 to < $135,000-$135,000 to < $155,000/QALY with the extent of benefit reduced (rROD of 61.5%). The PBAC considered these ICERs to be high, noting that the assumed 90% price reduction is highly unlikely to be realised, but acceptable. The PBAC noted that the ICER range for this population was lower than for the F/MF population and considered this appropriately reflected the difference in clinical need across the two populations, with the F/MF patients having a similarly severe phenotype to the F/F patients, but currently having no access to any CFTR modulator therapy.

5.14 The PBAC recalled that an ICER of around $155,000 to < $255,000/QALY had previously been accepted for the first generation CFTR modulator treatments – IVA for F/G, LUM/IVA for F/F and TEZ/IVA for F/F and F/RF populations. At the time of their listing, these treatments represented highly novel products for a condition with no other treatment options. The resulting prices for these were based on extremely optimistic assumptions in the economic model, including the assumption of a 90% price reduction at patent expiry as described above. This effectively means that the true ICER for these products has very likely been greater than previously estimated.

5.15 **F/G:** The PBAC considered that, consistent with the methodology proposed in the resubmission, it was reasonable for the cost of ELX/TEZ/IVA for the F/G population to be calculated as the weighted average price of that for the F/F and F/MF populations using weightings of 65.92% for the F/F population and 34.08% for the F/MF population.

5.16 Overall, given the substantial increase in cost for listing in the F/any population, the associated large opportunity cost, and that the 90% price reduction assumed in the economic model was inappropriate and very unlikely to be achieved, the PBAC considered that a price reduction would be required to ensure reasonable confidence that a high but acceptable ICER would be achieved.

5.17 The PBAC noted that the estimated patient numbers proposed in the resubmission were not aligned with the previous PBAC advice, which was that the F/F, F/RF and F/G groups should be based on previously agreed estimates for the listing of the available CFTR modulators on the PBS. Instead, the resubmission maintained a similar approach to the sponsor's prior submissions for ELX/TEZ/IVA. The PBAC maintained that the proposed discontinuation rates based on the trial data were very optimistic. Taking into account that actual rates of discontinuation for LUM/IVA and TEZ/IVA have been higher than estimated at time of listing (based on trial and extension study discontinuation rates), the PBAC considered that discontinuation rates based on applying the same proportional difference between the actual and estimated figures (see para 12.9 July 2021 PBAC PSD item 14.08) be applied to the ELX/TEZ/IVA studies – this would result in discontinuation rates of 2.6% at Year 1 and 7.3% at Year 2. The PBAC considered that the eligible patient estimates outlined in the resubmission could be accepted, in the context that: they represented the upper range of likely use based on the total eligible patients derived from the ACFDR numbers; and the sponsor had proposed a unit level rebate to achieve the cost-effective price, as opposed to an arrangement that relied on the estimates being realised in order to achieve a cost-effective price per patient (as for LUM/IVA and TEZ/IVA).

5.18 The PBAC advised that an RSA with subsidisation caps based at the level of the financial estimates should apply given the high financial impact, with a 100% reimbursement over the caps to ensure budget certainty.

5.19 The PBAC noted there were a number of data collection requirements associated with the proposed restriction (i.e., hospitalisations, FEV_1 measurement, weight and height); however, these measurements are not used to inform patient eligibility as set out in the restriction criteria. Further, these measurements are routinely collected as part of enrolment in the Australian Cystic Fibrosis Database Registry which has very high enrolment coverage of the CF population. The PBAC concluded this data collection and the inclusion of the prescribing instruction 'the patient must be registered in the Australian Cystic Fibrosis Database Registry' results in duplicate data collection that is unnecessary. As such, the PBAC advised the requirements for data collection may be removed from the restriction criteria. Further, the PBAC advised the prescribing instruction "For patients who have initiated non-PBS-subsidised treatment prior to [Insert listing date], date of initiating treatment, baseline FEV1 and hospitalisation dates prior to initiating treatment (where available) should be provided" may also be removed for consistency.

5.20 In addition to the removal of data collection requirements, the PBAC determined the following restriction amendments as proposed by the Secretariat are appropriate:

- include the following prescriber instruction: Trikafta is not PBS-subsidised for this condition in a patient who is currently receiving a strong CYP3A4 inducer as outlined in the Product Information.
- remove the requirement for submission of a pathology result with the authority application and require provision of i) name of pathology report provider, (ii) date of pathology report, (iii) unique identifying number/code that links the pathology result to the individual patient.

5.21 The PBAC considered all amendments to the restriction criteria could also be flowed onto the other CTFRm therapies, where relevant.

5.22 The PBAC advised that ELX/TEZ/IVA is not suitable for prescribing by nurse practitioners.

5.23 The PBAC advised that ELX/TEZ/IVA should not be exempt from the Early Supply Rule.

5.24 The PBAC advised, that under Section 101(3BA) of the *National Health Act 1953*, elexacaftor with tezacaftor and ivacaftor, and ivacaftor should not be treated as interchangeable on an individual patient basis with any other drug.

5.25 The PBAC found that the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation for ELX/TEZ/IVA:

a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over standard of care for some patients;

b) The treatment is expected to address a high and urgent unmet clinical need for some patients;

c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.

5.26 The PBAC noted that, given it made a positive recommendation, an Independent Review is not available for this decision.

Outcome:
Recommended

6 Recommended listing

6.1 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 100mg + tezacaftor 50mg + ivacaftor 75mg [56] (&) ivacaftor 150mg [28], 84	NEW (Public) NEW (Private)	1	1	5	Trikafta

Restriction Summary [new]	
	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 - at least one F508del mutation in the cystic fibrosis transmembrane conductance (CFTR) gene
	Indication: cystic fibrosis - at least one F508del mutation in the cystic fibrosis transmembrane conductance (CFTR) gene
	Treatment Phase: Initial 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
	Population criteria:
	Patients must be 12 years of age or older.
	Prescribing Instructions
	The patient must be registered in the Australian Cystic Fibrosis Database Registry.

	Trikafta is not PBS-subsidised for this condition in a patient who is currently receiving a strong CYP3A4 inducer as outlined in the Product Information.
	For the purposes of this restriction, PBS-subsidised 'CFTR modulator' means ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor and elexacaftor/ tezacaftor/ ivacaftor. 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; and (4) details of the name of the molecular testing for the patient having at least one F508del mutation including: (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
	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
	Administration Advice
	No increase in the maximum quantity or number of units may be authorised.
	No increase in the maximum number of repeats may be authorised
	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:
	Patients must be 12 years of age or older.
	Prescribing Instructions
	Trikafta is not PBS-subsidised for this condition in a patient who is currently receiving a strong CYP3A4 inducer as outlined in the Product Information.

	For the purposes of this restriction, PBS-subsidised 'CFTR modulator' means ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor and elexacaftor/ tezacaftor/ ivacaftor. 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.
	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
	Administration Advice
	No increase in the maximum quantity or number of units may be authorised.
	No increase in the maximum number of repeats may be authorised

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

Addendum to the December 2021 PBAC Minutes:

7 Background

7.1 Subsequent to the December 2021 meeting, the sponsor provided a listing proposal for ELX/TEZ/IVA to the Department. Following negotiations, the sponsor presented a pricing proposal for ELX/TEZ/IVA offering a weighted annual price of $[redacted] ($[redacted] per pack). The price proposed is higher than the price calculated based on the PBAC advice in December 2021, however it represents the lowest price for ELX/TEZ/IVA that the sponsor has offered to date. The sponsor also characterised this as its final offer.

7.2 The Department therefore sought PBAC advice, out of session in February 2022, as to whether the proposal from the sponsor was acceptable.

8 Details of proposal

8.1 Based on the December 2021 advice, the Department calculated that a weighted annual price (assuming 90% compliance) of $[redacted] would be consistent with the December 2021 PBAC advice. Vertex's latest offer is for an annual price of $[redacted]. Details of the calculated weighted prices as per the PBAC recommendation and as currently proposed are shown below. The weighted price calculations from the sponsor's December 2021 submission are presented in Table 2.

Table 7: Per PBAC recommendation (December 2021)

Population	F/F[1]	F/G[2]	F/MF[3]	F/RF and F/R117H[4]	Weighted cost per patient per year
%	53.23%	7.49%	27.51%	11.77%	
Cost per patient per year (assuming 90% compliance) ($)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

1. Assuming 25% reduction (0.75 x $[redacted]) (recommended reduction 25% to 30%)
2. Assuming 65.92% x F/F + 34.08% x F/MF cost
3. As recommended July 2021 PBAC meeting
4. Vertex calculated revised cost for TEZ/IVA following LUM/IVA and TEZ/IVA Managed Access Program consideration

Table 8: Per Vertex Pricing Proposal (17 February 2022)

Population	F/F	F/G[1]	F/MF	F/RF and F/R117H[2]	Weighted cost per patient per year
%	53.23%	7.49%	27.51%	11.77%	
Cost per patient per year (assuming 90% compliance) ($)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

1. Assuming 65.92% x F/F + 34.08% x F/MF cost
2. Vertex calculated revised cost for TEZ/IVA following LUM/IVA and TEZ/IVA Managed Access Program consideration

8.2 In its listing proposal, the sponsor claimed that due to an oversight, the delayed uptake of prevalent patients was not included in the submission to PBAC, and the sponsor has now included an adjustment in the model submitted to the Department that has a claimed impact of an additional 69 treated patients across 6 years.

8.3 Based on the Vertex patient estimates, at the price proposed, the 6 year net cost of listing, is $600 million to < $700 million, as shown below:

Table 9: Financial implications of listing ELX/TEZ/IVA on the PBS

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Cost to PBS ($)	[redacted][1]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Changed listing ($)	-[redacted][2]	-[redacted][3]	-[redacted][3]	-[redacted][3]	-[redacted][3]	-[redacted][1]
Net cost to PBS ($)	[redacted][3]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]

The redacted values correspond to the following ranges:
[1]$100 million to < $200 million
[2]$80 million to < $90 million
[3]$90 million to < $100 million
[4]$200 million to < $300 million

8.4 This is lower than the total net cost to PBS proposed in the sponsor's resubmission to the December 2021 PBAC meeting of $700 million to < $800 million over 6 years.

9 PBAC outcome

9.1 The PBAC noted that the sponsor's latest price offer for ELX/TEZ/IVA still resulted in very high ICERs, especially in relation to the F/MF and F/F populations (as previously outlined in the December 2021 PBAC advice). However, the PBAC advised that the sponsor's latest proposal was acceptable, taking into consideration the high clinical need for the treatment, particularly for those patients currently ineligible for a PBS-subsidised CFTR-modulator treatment; and recognising that ELX/TEZ/IVA was an effective treatment that provided a significant benefit for some patients.

10 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.

11 Sponsor's Comment

Vertex welcomes the positive recommendation made by the PBAC at their December Meeting for the listing of Trikafta® (elexacaftor/tezacaftor/ivacaftor and ivacaftor) for the treatment of Cystic Fibrosis (CF) patients aged 12 years and older who have at least one F508del mutation in the CFTR gene (F/any population).

From the time we made our first submission to the PBAC more than 12 months ago, Vertex has been advocating for PBS-funded access to Trikafta for all eligible CF patients. We are therefore pleased that every patient who could benefit from Trikafta is now included in this recommendation.