

## **6.02 ELEXACAFTOR WITH TEZACAFTOR AND WITH IVACAFTOR, AND IVACAFTOR**

**Pack containing 56 tablets elexacaftor 100 mg with  
tezacaftor 50 mg and with ivacaftor 75 mg and 28  
tablets ivacaftor 150 mg**

**Pack containing 56 tablets elexacaftor 50 mg with  
tezacaftor 25 mg and with ivacaftor 37.5 mg and 28  
tablets ivacaftor 75 mg**

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

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

**Trikafta<sup>®</sup>,**

**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 mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to ELX/TEZ/IVA based on clinical and/or *in vitro* assay data.
- 1.2 The extension to the population would include patients with:
  - 251 mutations deemed likely to respond to ELX/TEZ/IVA based on the Fischer Rat Thyroid (FRT) assay (177 mutations currently approved by the FDA, plus an additional 74 mutations)
  - 19 non-canonical splice mutations (which cannot be tested in the FRT assay) and
  - *N1303K* mutation (which does not show any effect of ELX/TEZ/IVA in the FRT assay).

The submission estimated that the expanded listing would provide access to ELX/TEZ/IVA for an additional 166 patients (in Year 1) of whom 32 have no current access to CFTR modulators.

- 1.3 Listing was requested based on the argument that it would be inequitable for patients with very rare mutations not to have access to ELX/TEZ/IVA and for these patients it is impractical to provide clinical evidence of efficacy. Listing was proposed at the current price of ELX/TEZ/IVA; no economic evaluation was presented in the submission to support the listing requested.

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

Component	Description
Population	CF patients aged 2 years of age or older with at least one mutation in the CFTR gene that is responsive to ELX/TEZ/IVA potentiation based on clinical data or in vitro assay
Intervention	ELX/TEZ/IVA
Comparator	IVA plus BSC for patients with mutations responsive to both IVA and ELX/TEZ/IVA TEZ/IVA plus BSC for patients with TEZ/IVA eligible residual function and splice mutations BSC for all other mutations
Outcomes	<ul style="list-style-type: none"> <li>• Absolute change from baseline in ppFEV1, where relevant</li> <li>• Absolute change from baseline in sweat chloride</li> <li>• Absolute change from baseline in nutritional status (weight, weight z-score, BMI, BMI z-score)</li> <li>• Absolute change from baseline in CFQ-R RD score</li> <li>• Measures of pulmonary exacerbations (PEX)</li> </ul>
Clinical claim	ELX/TEZ/IVA plus BSC is at least non-inferior and likely superior in terms of effectiveness compared with IVA plus BSC in patients with mutations responsive to both IVA and ELX/TEZ/IVA ELX/TEZ/IVA plus BSC is superior in terms of effectiveness compared with TEZ/IVA plus BSC in patients with TEZ/IVA eligible residual function and non-canonical splice mutations ELX/TEZ/IVA plus BSC is superior in terms of effectiveness compared with BSC in patients with all other mutations ELX/TEZ/IVA plus BSC is comparable in terms of safety compared to IVA + BSC, TEZ/IVA + BSC and BSC alone

Source: Table 1.2, p28 of the submission.

BSC = best supportive care; CFTR = cystic fibrosis transmembrane conductance regulator; ELX = elexacaftor; IVA, ivacaftor; TEZ = tezacaftor

## 2 Background

### Registration status

- 2.1 **TGA status at time of PBAC consideration:** not registered. The submission to the PBAC was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration, the first-round clinical evaluation report, the TGA Delegate’s Overview and the Advisory Committee on Medicines (ACM) minutes were available. The TGA Delegate was inclined to approve the extension of indications “...for the treatment of cystic fibrosis (CF) in patients aged 2 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene or a mutation in the CFTR gene that is responsive based on clinical and/or in vitro data.” (New addition underlined.)
- 2.2 The ACM considered ELX/TEZ/IVA to have an overall positive benefit-risk profile for the indication “For the treatment of those who meet the diagnostic criteria of cystic fibrosis (CF) in patients aged 2 years and older who have at least one mutation in the

cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive, based on clinical study or *in vitro* evidence". The ACM supported the extension of indication without a restrictive list of specific variants.

- 2.3 The pre-PBAC response noted the ACM supported the extension of the ELZ/TEZ/IVA indication without a restrictive list of specific CFTR variants and requested the PBS listing for ELX/TEZ/IVA be aligned with the TGA approval to ensure equitable and timely access for all patients who could benefit from treatment.

### Previous PBAC consideration

- 2.4 A summary of the current PBS populations for CFTR modulators is summarised in Table 2.

**Table 2 Current PBS populations for CFTR modulators**

	Lumacaftor/ ivacaftor	Ivacaftor	Elexacaftor/tezacaftor/ ivacaftor	Tezacaftor/ ivacaftor
Age	Over 1 year of age	Over 4 months of age <sup>1</sup>	Over 2 years of age	Over 12 years of age <sup>2</sup>
Current PBS population	Homozygous for the F508del mutation (F/F population)	At least one G551D mutation or at least one Class III mutation or at least one mutation that is responsive to ivacaftor based on clinical and/or <i>in vitro</i> assay data.	Heterozygous for the F508del mutation (F/any population)	Homozygous for the F508del mutation (F/F population) or at least one RF mutation

CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane regulator; F = F508del mutation; PBAC = pharmaceutical benefits advisory committee; RF = residual function.

- Listing for patients over one month of age was considered at the March 2025 PBAC meeting
- TEZ/IVA is TGA indicated for the treatment of patients with CF aged 6 years and older who are homozygous for the F508del mutation or who have at least one mutation in the CFTR gene that is responsive to TEZ/IVA based on *in vitro* data and/or clinical evidence.

## 3 Requested listing

- 3.1 The submission proposed initial and continuing restrictions for patients 2 to 5 years and those older than 6 years. The restriction for initial and continuing treatment for patients older than 6 years of age is shown below.

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty <sup>1</sup>	Max. Qty units	Number of Repeats	Available brands
Elexacaftor/tezacaftor/ivacaftor				
Elexacaftor 100 mg/ tezacaftor 50 mg/ ivacaftor 75 mg tablets co-packaged with ivacaftor 150 mg tablets	\$21,375.00 published price ■ effective price	Pack containing 56 tablets and 28 tablets, (4 weeks supply)	5	Trikafta®, Vertex Pharmaceuticals (Australia) Pty Ltd
Elexacaftor 50 mg/ tezacaftor 25 mg/ ivacaftor 37.5 mg tablets co-packaged with ivacaftor 75 mg tablets	\$21,375.00 published price ■ effective price	Pack containing 56 tablets and 28 tablets, (4 weeks supply)	5	

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Elexacaftor 100 mg/ tezacaftor 50 mg/ ivacaftor 75 mg granules co-packaged with ivacaftor 75 mg granules	\$21,375.00 published price █ effective price	Pack containing 28 sachets and 28 sachets (4 weeks supply)	5	
Elexacaftor 80 mg/ tezacaftor 40 mg/ ivacaftor 60 mg granules co-packaged with ivacaftor 59.5 mg granules	\$21,375.00 published price █ effective price	Pack containing 28 sachets and 28 sachets (4 weeks supply pack)	5	

1. Public hospital DPMQ presented

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<b>Category / Program:</b> Section 100 – Highly Specialised Drugs Program
<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/>
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (in writing only via post/HPOS upload)
<b>Condition:</b> Cystic fibrosis
<b>Indication:</b> Cystic fibrosis
<b>Treatment Phase:</b> Initial treatment
<b>Clinical criteria:</b> Patient must have at least one mutation in the CFTR gene that is responsive to elexacaftor/tezacaftor/ivacaftor potentiation based on clinical and/or in vitro assay data
<b>AND</b>
<b>Clinical criteria:</b> The treatment must be given concomitantly with standard therapy for this condition
<b>AND</b>
<b>Clinical criteria:</b> Patient must have either chronic sinopulmonary disease or gastrointestinal and nutritional abnormalities, prior to initiating treatment with this drug
<b>Treatment criteria:</b> 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
<b>AND</b>
<b>Treatment criteria:</b> 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
<b>Population criteria:</b> Patient must be at least 6 years of age
<b>Prescribing Instructions:</b> For the purposes of this restriction, the list of mutations considered to be responsive to elexacaftor/tezacaftor/ivacaftor is defined in the TGA approved Product Information
<b>Prescribing Instructions:</b> 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.
<b>Prescribing Instructions:</b> The authority application must be in writing and must include: (1) a completed authority prescription; and (2) a completed Cystic Fibrosis Authority Application Supporting Information Form; and (3) details of the pathology report substantiating the specific mutation considered to be responsive to elexacaftor/tezacaftor/ivacaftor as listed in the TGA approved PI - quote each of the: (i) the specific mutation listed in the TGA approved PI (ii) name of the pathology report provider, (iii) date of pathology report, (iv) unique identifying number/code that links the pathology result to the individual patient; and (4) current CYP3A4 inhibitors, CYP3A4 inducers and IV antibiotics
<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
<b>Administrative Advice:</b> <b>No increase in the maximum</b> number of repeats may be authorised.
<b>Administrative Advice:</b> Special Pricing Arrangements apply.
<b>Administrative Advice:</b> For the purposes of this restriction, PBS-subsidised 'CFTR modulator' means ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor and elexacaftor/ tezacaftor/ ivacaftor.

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**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](http://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](http://www.servicesaustralia.gov.au/hpos)

Or mailed to:

Services Australia

Complex Drugs

Reply Paid 9826

HOBART TAS 7001

<b>Category / Program:</b> Section 100 – Highly Specialised Drugs Program
<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/>
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (in writing only via post/HPOS upload)
<b>Condition:</b> Cystic fibrosis
<b>Indication:</b> Cystic fibrosis
<b>Treatment Phase:</b> Continuing treatment
<b>Clinical criteria:</b> Patient must have previously received PBS-subsidised treatment for this condition
<b>AND</b>
<b>Clinical criteria:</b> The treatment must be given concomitantly with standard therapy for this condition
<b>AND</b>
<b>Treatment criteria:</b> 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
<b>AND</b>
<b>Treatment criteria:</b> 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
<b>Population criteria:</b> Patient must be at least 6 years of age
<b>Prescribing Instructions:</b> 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.
<b>Prescribing Instructions:</b> The authority application must be in writing and must include: (1) a completed authority prescription; 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

3.2 The proposed restrictions are essentially the same as the existing restrictions, with the cross reference to the TGA list of approved mutations as the basis for eligibility of

patients. The PBAC noted the ACM was supportive of not including a restrictive list of specific variants.

- 3.3 The pre-PBAC response requested that the lower dose tablet formulation containing ELX 50mg, TEZ 25 mg, IVA 37.5mg and IVA 75mg (56 tablets) be made available on the PBS for patients aged 2 to <5 years. The pre-PABC response stated that many young children with CF take tablets routinely as part of CF best supportive care, and therefore, tablets provide them with a more convenient treatment option over granules.

## 4 Population and disease

- 4.1 CF is a rare genetic disease that is caused by mutations in the CFTR gene which impair ion transport across epithelial membranes, causing thick mucus to accumulate within the lungs and obstructing the function of the liver, pancreas, and other organs, resulting in significant morbidity, reduced quality of life and premature mortality.
- 4.2 CFTR modulators (CFTRm) have been used to treat CF for the last 10 years or more. Initially, clinical trial evidence was used to establish the efficacy of ivacaftor for disease caused by the G551D mutation, but, over time, the number of mutations thought to be responsive to treatment has expanded and the list now includes rare mutations.
- 4.3 As there is no clinical efficacy data for CFTRm use for many of these mutations, registration by the US FDA has been based on *in vitro* evidence that the drugs increase chloride transport by CFTR affected by each mutation. The criterion chosen by the FDA to define a positive result in *in vitro* testing was an increase of chloride transport of at least 10% of normal, which was based only on the observation that mutations allowing 10% of normal CFTR activity are associated with minimal clinical disease. Treatment of some mutations has been approved despite their not meeting the *in vitro* criteria.<sup>1</sup>
- 4.4 Not all mutations can be tested in the accepted *in vitro* assay, including splice mutations. For these mutations listing was proposed based on clinical data.
- 4.5 The submission proposed that all mutations which respond *in vitro* can be assumed to respond to ELX/TEZ/IVA, but that some mutations which do not respond *in vitro* may also respond to ELX/TEZ/IVA (i.e., N1303K mutation). The submission presented clinical data for the N1303K mutation, which is relatively common, and implied that other, rare mutations for which there is no clinical data could also be listed.
- 4.6 Because *in vitro* results may not predict clinical response, some clinicians have suggested a trial of CFTRm treatment in all patients with cystic fibrosis. This approach is the basis of the French compassionate access program, and the submission suggests that it could be adopted by the PBAC: “PBAC may wish to consider whether an alternative approach is warranted to allow treatment of patients with very rare or

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<sup>1</sup> Costa E, Girotti S, Pauro F, Leufkens HGM, Cipolli M. The impact of FDA and EMA regulatory decision-making process on the access to CFTR modulators for the treatment of cystic fibrosis. *Orphanet J Rare Dis* 2022, <https://doi.org/10.1186/s13023-022-02350-5>

unknown mutations that have not yet been tested in the FRT cell studies but may be responsive to ELX/TEZ/IVA”.

- 4.7 However, the evaluation noted the French program allows ongoing treatment only in patients who demonstrate a response ELX/TEZ/IVA, and it was not clear from the current submission whether the sponsor envisages a requirement for evidence of response as part of a program for mutation-agnostic treatment.

## 5 Comparator

5.1 The submission proposed different comparators, depending on the mutation and existing listings for CFTRm drugs, as summarised in Table 3:

- For patients aged  $\geq 2$  years, with one of 92 mutations responsive to IVA (including gating and residual function (RF) mutations) – the comparator proposed was IVA + best supportive care (BSC);
- For patients aged  $\geq 12$  years with one of 20 RF mutations and who are currently eligible for both IVA and TEZ/IVA - the comparator proposed was TEZ/IVA + BSC;
- For patients aged  $\geq 12$  years, with one of 5 non-canonical splice mutations who are currently eligible for TEZ/IVA but not IVA - the comparator proposed was TEZ/IVA + BSC;
- For patients aged 2 years and older, without either IVA responsive or TEZ/IVA responsive mutations, but with a mutation responsive to ELX/TEZ/IVA – the comparator proposed was BSC.

Table 3: Comparator

Population	Comparator	# mutations <sup>1</sup>
Over 2 years of age, IVA responsive	IVA	9 gating 24 RF (to 11 years of age for some RF mutations) 59 IVA responsive
Over 12 years of age, RF mutations	TEZ/IVA	20 RF <sup>2</sup>
Over 12 years of age, non-canonical mutations	TEZ/IVA	5 non-canonical
Over 2 years of age, additional ELX/TEZ/IVA responsive	BSC	14 non-canonical 1 N1303K 159 ELX/TEZ/IVA responsive

<sup>1</sup>Total mutations = 271 = 9 + 24 + 59 + 5 + 14 + 1 + 159

<sup>2</sup>Assumed patients over 12 years of age would be treated with TEZ/IVA (rather than IVA)

## 6 Consideration of the evidence

### Sponsor hearing

6.1 There was no hearing for this item.

### Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (34) and organisations (3) via the Consumer Comments facility on the PBS website. The comments from

individuals that have used ELX/TEZ/IVA noted the increased lung function, reduced infections and hospital visits associated with ELX/TEZ/IVA. The comments from individuals that would like access to ELX/TEZ/IVA emphasised the significant impact CF has on quality of life and daily living for patients and their families. Many individuals noted the inequity of access for CF patients with rare mutations and the high financial burden of self-funding ELX/TEZ/ IVA.

- 6.3 Cystic Fibrosis Australia noted the available clinical evidence for ELZ/TEZ/IVA supports its efficacy and safety in this population and the importance of providing early access to reduce long term damage. CF Together suggested flexible PBS listing criteria would be appropriate that included responsive and non-categorised mutations and proposed a clinical assessment approach to determine the efficacy of ELX/TEZ/IVA for individuals with rare mutations. The National Paediatric Medicines Form also expressed their support for listing ELX/TEZ/IVA for this population. All organisations noted the equity issues for people with rare mutations and the prohibitive cost of paying for ELX/TEZ/IVA privately.

### Clinical studies

- 6.4 The clinical evidence presented was grouped by the submission according to the groups of mutations proposed for listing. The data sources proposed to support each group of mutation are summarised in Table 4.

**Table 4: Data source for mutations included in current submission**

Mutation group	Data source/rationale
177 FRT mutations (previously FDA approved)	<i>In vitro</i> data using FRT system (Study P289) Study 124 Phase 3 RCT data Study CFD-016 RWE data Indicated for IVA and/or TEZ/IVA
<i>N1303K</i>	Solomon et al. 2023 Sadras et al. 2023 Livnat et al. 2023 Burgel et al. 2024
5 non-canonical splice mutations	Extrapolation based on IVA and TEZ/IVA clinical data Study 124 Phase 3 RCT data Study CFD-016 RWE data
14 additional non-canonical splice mutations	Extrapolation based on mode of action and response of non-canonical splice mutations in Study 124
74 additional mutations based on FRT	<i>In vitro</i> data using FRT system (Study U032) Burgel et al. 2024

Source: Table 1.1, p 27 of the submission.

FDA, Food and Drug Administration; FRT, Fischer Rat Thyroid; IVA, ivacaftor; RWE, real-world evidence; TEZ/IVA, tezacaftor/ivacaftor.

- 6.5 Details of the studies presented in the submission are provided in Table 5.

**Table 5: Studies and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Clinical studies</b>		
Study 124 VX21-445-124 NCT05274269	Study 124 Clinical Study Report. A Phase 3 Double-blind, Randomized, Placebo-controlled Study Evaluating the Efficacy and Safety of ELX/TEZ/IVA in Cystic Fibrosis Subjects 6 Years of Age and Older With a Non-F508del ELX/TEZ/IVA-responsive CFTR Mutation. Castellani C, et al. Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor (ELX/TEZ/IVA) in People with Cystic Fibrosis and ELX/TEZ/IVA-responsive, Non-F508del Genotypes: A Phase 3, Randomised, Placebo-Controlled Trial.	Version 1.0 06 October 2023  47th European Cystic Fibrosis Conference; 5-8 June 2024
Study 125 VX21-445-125 NCT05331183	Study 125 Key Results Memo. A Phase 3 Open-label Study Evaluating the Long-term Safety and Efficacy of ELX/TEZ/IVA in Cystic Fibrosis Subjects With Non-F508del CFTR Genotypes	10 July 2024
Solomon et al 2023.	Solomon GM. Interim results of an open-label trial to evaluate ETI in individuals with cystic fibrosis and an N1303K mutation who are not eligible for modulator treatment.	NACFC; 3 November 2023
Sadras et al, 2023	Sadras I, et al. Clinical and functional efficacy of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis carrying the N1303K mutation	<i>Journal of Cystic Fibrosis</i> 2023;22:1062-1069
<b>Real-world evidence</b>		
Study CFD-016 VX22-CFD-016	Study CFD-016 Clinical Study Report. An Observational Study Evaluating Real-world Clinical Outcomes of Elexacaftor/Tezacaftor/Ivacaftor Treatment in People With Cystic Fibrosis Who Have an Elexacaftor/Tezacaftor/Ivacaftor-responsive non-F508del CFTR Genotype. Mahic M, et al. Real-World Effectiveness of Elexacaftor/Tezacaftor/Ivacaftor (ELX/TEZ/IVA) in People with Cystic Fibrosis and ELX/TEZ/IVA-Responsive, Non-F508del CFTR Genotypes.	Version 1.0 19 October 2023  47th European Cystic Fibrosis Conference; 5-8 June 2024.
French compassionate access program	Burgel P-R, et al. The French compassionate programme of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis with advanced lung disease and no F508del CFTR variant. Burgel P-R, et al. The expanded French compassionate programme for elexacaftor-tezacaftor-ivacaftor use in people with cystic fibrosis without a F508del CFTR variant: a real-world study. Dreano E, et al. Theratyping cystic fibrosis patients to guide elexacaftor/tezacaftor/ivacaftor out-of-label prescription.	European Respiratory Journal 2023;61:2202437  The Lancet Respiratory Medicine 2024; <a href="https://doi.org/10.1016/S2213-2600(24)00208-X">https://doi.org/10.1016/S2213-2600(24)00208-X</a>  European Respiratory Journal 2023;62:2300110
Cromwell et al, 2024.	Cromwell EA, et al. Impact of the expanded label for elexacaftor-tezacaftor-ivacaftor in people with cystic fibrosis with no F508del variant in the United States.	European Respiratory Journal 2024; Sep 3:2401146. doi: 10.1183/13993003.01146-2024
Livnat et al, 2023.	Livnat G, et al. Treatment effects of Elexacaftor/Tezacaftor/Ivacaftor in people with CF carrying non-F508del mutations.	<i>Journal of Cystic Fibrosis</i> 2023;22:450-455

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Trial ID	Protocol title/ Publication title	Publication citation
<b>Supporting evidence</b>		
Lupas et al 2024	Lupas D, et al. The clinical effectiveness of elexacaftor/tezacaftor/ivacaftor (ETI) for people with CF without a F508del variant: A systematic review and meta-analysis.	Journal of Cystic Fibrosis 2024; <a href="https://doi.org/10.1016/j.jcf.2024.07.012">https://doi.org/10.1016/j.jcf.2024.07.012</a>
<b>In vitro studies</b>		
Study P289*	P289 Nonclinical Study Report. In Vitro Pharmacological Profiling of CFTR Mutations in FRT Cells Using VX-445, TEZ, and IVA: Effects on Processing and Trafficking, and Chloride Transport.	Version 4.0. 6 November 2024
Study U032*	U032 Nonclinical Study Report. In Vitro Pharmacological Profiling of CFTR Mutations in FRT Cells Using Elexacaftor (ELX; VX-445), Tezacaftor (TEZ; VX-661), and Ivacaftor (IVA; VX-770): Effects on CFTR Processing and Trafficking and Cl- Transport	5 February 2024

Source: Table 2.3, pp57-58 of the submission.

\* Not discussed further herein

6.6 The key features of the included evidence are summarised in Table 6.

**Table 6: Key features of the included evidence**

Study	Design	Risk of bias	Population	Outcomes
VX21-445-124 <sup>1</sup> N = 307	R, DB, MC (84 sites, Europe & Canada); randomised 2:1 to ETI or placebo, 24wk	Low	CF aged ≥ 6 yrs with ppFEV <sub>1</sub> ≥ 40% and ≤100%, at least one of 15 prespecified non-F508del ETI-responsive mutations, or one of 5 non-canonical splice mutations.	Primary: Change in ppFEV <sub>1</sub> at 24wk active vs placebo; Secondary: Change in SwCl, CFQ-R RD, BMI, infective exacerbations at 24 wk active vs placebo
CFD-016 N = 422	Retrospective study of US CF registry patients initiating ETI between 21 October 2019 and 1 December 2022; data cut-off 31 December 2022	High	CF aged ≥ 6 yrs, at least one ETI-responsive mutation and no F508del mutation; at least one ppFEV <sub>1</sub> in the 12 months before initiating ETI and at least one at least 4 wk after initiation; ppFEV <sub>1</sub> before ETI (mean if > 1 measurement) ≥30% and ≤100%	Primary: Change in ppFEV <sub>1</sub> ; Secondary: Change in weight and BMI
Cromwell, 2024 N = 573	Retrospective study of US CF registry patients (ie, same registry as CFD-016) eligible for ETI with data cut-off 31 December 2022.	High	CF aged ≥ 6 yrs, at least one ETI-responsive mutation and no F508del mutation	NA
Solomon, 2023 <sup>2</sup> N = 20	Prospective observational, 2-centres, 28d	High	CF aged >12yrs, with N1303K + another minimal function mutation not eligible for ETI (homozygous N1303K was eligible but no patients were recruited)	Primary: Change in SwCl Secondary: Change in ppFEV <sub>1</sub> , weight, CFQ-R RD

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Sadras, 2023 N = 8	Prospective observational, single centre, 8wk	High	CF homozygous N1303K (2) or N1303K + another nonsense or frameshift mutation (6); treated with ETI provided by private insurance or private purchase	NA
Livnat, 2023 N = 16	Retrospective case series, not clear if consecutive; five centres; 3-6mo treatment	High	CF, aged $\geq 12$ yrs, no F508del, treated with ETI; 6 with G85E, 6 with D1152H, 1 with N1303K	NA
Burgel, 2024 N = 479	Prospective observational; consecutive patients referred to French Compassionate Access Program. Between 22 May 2022 and 1 June 2023 required ppFEV <sub>1</sub> < 40 or consideration of transplant, then no severity requirement. 4-6wk treatment.	High	CF aged $\geq 12$ yrs (19% <18); no F508del; 479 total, 443 not receiving CFTRm; 83 had at least one FDA-approved mutation, 360 had no FDA-approved mutation.	NA

Source: Constructed during the evaluation from published reports. BMI = body mass index; CF = cystic fibrosis; CFQ-R RD = Cystic Fibrosis Questionnaire-Revised respiratory domain; CFTRm = cystic fibrosis transmembrane conductance regulator modifier; DB = double blind; ETI = elexacaftor/tezacaftor/ivacaftor; MC = multicentre; NA = not applicable; ppFEV<sub>1</sub> = percent predicted forced expiratory volume in one second; R = randomised; SwCl = sweat chloride.

1 This Study 124 is not the Study 124 considered by PBAC in November 2023. 2 Data provided only as a Powerpoint presentation.

## Comparative effectiveness

- 6.7 The evidence in the submission was a mixture of clinical evidence based on outcomes previously considered by the PBAC as well as *in vitro* data. The PBAC has previously accepted change in ppFEV<sub>1</sub> as establishing evidence of efficacy (para 6.19, lumacaftor/ivacaftor Public Summary Document (PSD), July 2019 PBAC Meeting, para 6.18, ivacaftor PSD, March 2018 PBAC Meeting) and that changes in sweat chloride provide evidence of biological activity (para 6.22, ivacaftor PSD, March 2019 PBAC meeting).
- 6.8 The submission suggested that any increase in ppFEV<sub>1</sub> equal to or greater than the usual annual rate of decline - 1-3% - is clinically important. A clinically significant change in ppFEV<sub>1</sub> of 10 percentage points has been previously used as the MCID by PBAC (para 6.10, ELX/TEZ/IVA PSD, November 2022 PBAC Meeting with March 2023 Addendum; para 6.22, ivacaftor PSD, November 2023 PBAC Meeting).
- 6.9 The submission proposed listing of ELX/TEZ/IVA for patients with *N1303K* mutation. This mutation does not respond in the FRT assay and most patients treated with ELX/TEZ/IVA do not show a fall in sweat chloride, so the questions of the clinical relevance or of the MCID for sweat chloride are irrelevant in relation to this submission.
- 6.10 The key results from Study 124 (VX21-445-124) are shown in Table .

6.11 In the population as a whole, ELX/TEZ/IVA treatment was associated with statistically significant decreases in sweat chloride and increases in ppFEV<sub>1</sub>, CFQ-RD R scores and BMI. The effect size was similar in the population as a whole and in the pre-specified mutation subgroups. The effect sizes were similar to those seen in the clinical trials of ivacaftor for responsive mutations, where ppFEV<sub>1</sub> increased by 10-12 percentage points.

**Table 7: Efficacy Outcomes in Trial VX21-445-124**

	<b>Placebo N = 102</b>	<b>ETI N = 205</b>	<b>LS Mean Difference (95% CI)</b>
ppFEV <sub>1</sub> Baseline, mean (SD) Change to 24 wk, LS mean (95% CI)	68.1 (18.1) -0.4 (-2.0, 1.3)	67.5 (17.6) 8.9 (7.7, 10.0)	9.2 (7.1, 11.3)
Sweat Chloride Baseline, mean (SD) Change to 24wk, LS mean (95% CI)	75.2 (28.7) 0.5 (-2.6, 3.6)	79.5 (26.9) -27.8 (-30.0, -25.6)	-28.3 (-32.1, -24.5)
BMI Baseline, mean (SD) Change to 24wk, LS mean (95% CI)	22.5 (4.2) 0.35 (0.16, 0.53)	22.4 (4.6) 0.81 (0.68, 0.94)	0.47 (0.24, 0.69)
CFQ-R RD Score Baseline, mean (SD) Change to 24wk, LS mean (95% CI)	65.8 (21.3) -2.0 (-5.2, 1.3)	64.1 (20.7) 17.5 (15.2, 19.8)	19.5 (15.5, 23.5)
Pulmonary Exacerbations Subjects with Events, n (%) Number of Events Annualised Event Rate	26 (25.5%) 40 0.63	18 (8.8%) 21 0.17	NR
	<b>Patients with FRT- responsive mutations N = 69<sup>1</sup></b>	<b>Patients with FRT- responsive mutations N = 129<sup>1</sup></b>	
ppFEV <sub>1</sub> Baseline, mean (SD) Change to 24 wk, LS mean (95% CI)	70.9 (16.7) -0.7 (-2.4, 1.0)	70.1 (17.4) 8.7 (6.8, 10.6)	NR
Sweat Chloride Baseline, mean (SD) Change to 24wk, LS mean (95% CI)	74.7 (28.0) 1.2 (-0.6, 3.0)	78.1 (28.1) -35.4 (-39.0, -31.8)	NR
CFQ-R RD Score Baseline, mean (SD) Change to 24wk, LS mean (95% CI)	66.9 (19.9) -2.6 (-5.6, 0.4)	65.0 (20.4) 17.4 (14.0, 20.7)	NR
	<b>Subjects with Splice Mutations N = 34<sup>1</sup></b>	<b>Subjects with Splice Mutations N = 82<sup>1</sup></b>	
ppFEV <sub>1</sub> Baseline, mean (SD) Change to 24 wk, LS mean (95% CI)	61.6 (19.8) -0.1 (-2.4, 2.6)	64.0 (17.0) 8.9 (6.9, 10.8)	NR
Sweat Chloride Baseline, mean (SD) Change to 24wk, LS mean (95% CI)	76.0 (30.0) -0.8 (-2.8, 1.2)	79.3 (26.4) -15.4 (-17.7, -13.1)	NR
CFQ-R RD Score Baseline, mean (SD) Change to 24wk, LS mean (95% CI)	62.4 (24.6) -0.5 (-5.7, 4.7)	62.4 (21.4) 17.7 (13.5, 22.0)	NR

Source: VX21-445-124 CSR: Table 11-2, p51; Table 11-3, p53; Table 11-4, p55; Table 11-5, p57; Table 11-7, p61; Table 11-11, p66; Table 11-12, p67.

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CFQ-R RD = Cystic Fibrosis Questionnaire–Revised respiratory domain; CFTR = cystic fibrosis transmembrane conductance regulator; FRT = Fisher rat thyroid; LS = least squares; NR = not reported; ppFEV<sub>1</sub> = percent predicted forced expiratory volume in one second; SD = standard deviation.

1 Numbers in the FRT-responsive mutation and splice mutation subgroups do not add to 102 and 205 because patients with an FRT-responsive mutation and a splice mutation were included in both groups (p69 of the submission).

6.12 The key results from Study CFD-106 and Cromwell 2024 are shown in Table 8. While reported separately in the submission, it appears that Study CFD-016 (published as Mahic, 2024) and Cromwell, 2024 report essentially the same patients, with the slight differences shown in Table 8.

6.13 Mean and median increases in ppFEV<sub>1</sub> in these patients were small. In CFD-016 response was highly variable, from marked deterioration to marked improvement, and close to 50% of patients recorded a fall in ppFEV<sub>1</sub> during ELX/TEZ/IVA treatment.

**Table 8: Changes in ppFEV<sub>1</sub> with ETI treatment in study CFD-016 and Cromwell, 2024**

	ppFEV <sub>1</sub> at Baseline	Change in ppFEV <sub>1</sub> to End of Treatment
<b>CFD-016 All Patients, N = 352</b>		
Mean (SD)	75.8 (18.0)	4.5 (9.8)
95% CI	73.9, 77.6	3.5, 5.6
Median (range)	80.6 (31.3, 100)	2.8 (-31.7, 59.2)
<b>CFD-016 CFTRM Naïve, N = 154</b>		
Mean (SD)	76.4 (17.5)	6.11 (10.7)
95% CI	73.6, 79.2	4.4, 7.8
Median (range)	80.8 (32.1, 99.8)	4.4 (-20.4, 59.2)
<b>CFD-016 CFTRm Treated, N = 197</b>		
Mean (SD)	75.4 (18.2)	3.3 (9.0)
95% CI	72.9, 78.0	3.5, 5.6
Median (range)	80.6 (31.3, 100)	2.4 (-31.7, 54.8)
<b>Cromwell, 2024, All Patients with ppFEV<sub>1</sub> data, N = 546</b>		
Median (IQR)	85.6 (61.8, 99.0)	-
Model Estimated Mean Difference, (95% CI) <sup>1</sup>	-	3.4 (2.1, 4.6)
<b>Cromwell, 2024, Patients with ppFEV<sub>1</sub> data CFTRm Naïve, N = 231</b>		
Median (IQR)	84.0 (59.8, 97.3)	-
Model Estimated Mean Difference, (95% CI) <sup>1</sup>	-	4.6 (2.8, 6.4)
<b>Cromwell, 2024, Patients with ppFEV<sub>1</sub> data CFTRm Treated, N = 315</b>		
Median (IQR)	86.8 (63.4, 101.0)	-
Model Estimated Mean Difference, (95% CI) <sup>1</sup>	-	2.4 (0.7, 4.1)

Source: VX22-CFD-016 CSR, Table 11-1, p18; Table 11-4, p22; Cromwell, 2024, Table 3.

<sup>1</sup> Linear regression with ppFEV<sub>1</sub>, BMI and BMI percentile.

CI = confidence interval; ppFEV<sub>1</sub> = percent predicted forced expiratory volume in one second; SD = standard deviation.

6.14 The key results from Burgel 2024, which were from patients eligible for a trial of ELX/TEZ/IVA under the French national compassionate access scheme are shown in Table 7. The submission proposed that this study supported use in patients with N1303K and 74 additional mutations based on FRT.

**Table 7: Changes in sweat chloride and ppFEV<sub>1</sub> in Burgel, 2024 according to responder status and FDA-approved mutation**

	Non-responders with no FDA-approved CFTR mutation N = 183	Responders with no FDA-approved CFTR mutation N = 177	Responders with ≥1 FDA-approved CFTR mutation N = 81	Patients receiving ivacaftor at initiation of ETI N = 36
Sw Cl at baseline, mM, median (IQR)	103 (94 - 110)	96 (81 - 106)	81 (61 - 101)	30 (21 - 42)
Change in Sw Cl, mean (95% CI)	-1.8 (-3.9, 0.3)	-20.5 (-17.2, -23.8)	-44.5 (-39.1, -49.8)	-11.2 (-15.0, -7.5)
Patients with decrease in Sw Cl ≥ 20 mmol/L, n (%)	11 (6%)	74 (42%)	68 (84%)	10 (28%)
ppFEV <sub>1</sub> at baseline, median (IQR)	65 (42 - 82)	65 (45 - 86)	72 (43 - 95)	53 (33 - 78)
Change in ppFEV <sub>1</sub> , mean (95% CI)	1.6 (0.5, 2.8)	13.2 (11.4, 15.0)	11.1 (8.4, 13.7)	4.9 (2.0, 7.7)
Patients with increase in ppFEV <sub>1</sub> ≥ 10, n (%)	23 (13%)	96 (54%)	40 (49%)	5 (14%)

Source: Table 2, Burgel et al, 2024, *Lancet Respir Med*, <https://doi.org/10.1016/>

<sup>1</sup> Data for "Non-responders with an FDA-approved CFTR mutation" were not provided in the published paper because only two of 83 patients with FDA-approved mutations were classified as non-responders.

CFTR = cystic fibrosis transmembrane conductance regulator; CI = confidence interval; ETI = elexacaftor/tezacaftor/ivacaftor; FDA = US Food and Drug Administration; IQR = inter-quartile range; ppFEV<sub>1</sub> = percent predicted forced expiratory volume in one second; Sw CL = sweat chloride.

- 6.15 The results of the three small case series, presented primarily to support the listing of the *N1303K* mutation are presented in Table 8.
- 6.16 Solomon, 2023, reported results of ELX/TEZ/IVA treatment in 20 patients with *N1303K* and another minimal function mutation not currently eligible for ELX/TEZ/IVA treatment (patients homozygous for *N1303K* were eligible for inclusion but none were recruited). Sadras, 2023 reported results in two patients homozygous for *N1303K* and six heterozygous for *N1303K* and another nonsense or frameshift mutation. Livnat, 2023, reported results in 16 patients who did not have a *F508del* mutation; six had *G85E* and six had *D1152H*; only one had *N1303K*.

**Table 8: Results of the small case series**

	Change in Sweat Chloride at longest treatment date, mmol/L	Patients with Fall in Sweat Chloride ≥ 20 mmol/L	Change in ppFEV <sub>1</sub> at longest treatment date	Number (%) of Patients with Change in ppFEV <sub>1</sub> > 10
	Mean (95% CI)	n (%)	Mean (95% CI)	n (%)
Solomon, 2023 N = 20	0.9 (-1.9, 3.8)	1 (5%)	9 (6.1, 11.9)	9 (45%)
Sadras, 2023 N = 8	-7 (NR)	1 (12.5%)	18.4 (NR)	6 (75%)
Livnat, 2023, patient with <i>N1303K</i> N = 1	-83 (NA)	1 (100%)	11 (NA)	1 (100%)

Source: Constructed during the evaluation from published reports.

6.17 The results of Sadras and Livnat are of limited value, because of the lack of statistical analysis and small numbers. The results of Solomon, 2023 are consistent with those of Burgel, 2024, in finding minimal effects of ELX/TEZ/IVA on sweat chloride in patients with *N1303K*, and a clinically significant rise in ppFEV<sub>1</sub> in roughly half the patients.

### Comparative harms

6.18 Adverse event data were only provided for Study 124 and are shown in Table 9.

Table 9: Adverse Events in VX21-445-124

	Placebo N = 102	ETI N = 205
Exposure Duration, wk, Median (range)	24 (22.6, 25.9)	24 (1.6, 26.3)
Subjects with any AE	97 (95.1%)	193 (94.1%)
Subjects with any SAE	15 (4.7%)	18 (8.8%)
Subjects with any treatment-related AE	29 (28.4%)	125 (61%)
Treatment discontinuation due to AE, n (%)	0	5 (2.4%)
Treatment interruption due to AE, n (%)	1 (1.0%)	25 (12.2%)
AE leading to death, n (%) <sup>1</sup>	0	1 (0.5%)
Rash, n (%)	3 (2.9%)	55 (26.8%)
Moderate	1 (1.0%)	23 (11.2%)
Severe	0	5 (2.4%)
Leading to treatment discontinuation	0	1 (0.5%)
Leading to treatment interruption	0	15 (7.3%)
Alanine aminotransferase >ULN, n (%)		
≤3 x ULN	13 (12.7%)	38 (18.5%)
>3 x ULN	0	10 (4.9%)
Aspartate aminotransferase >ULN, n (%)		
≤3 x ULN	16 (15.7%)	42 (20.5%)
>3 x ULN	0	10 (4.9%)
Total bilirubin >ULN, n (%)		
≤1.5 x ULN	7 (6.9%)	33 (16.1%)
>1.5 x ULN	4 (3.9%)	14 (6.8%)

Source: VX21-445-124 CSR: Table 12-1, p69; Table 12-2, pp70-71; Table 12-5, pp75-76; Table 12-6, pp77-79.

AE = adverse event; SAE = serious adverse event; ULN = upper limit of normal.

<sup>1</sup> The cause of death was lung cancer.

6.19 As in previous studies, rash and liver abnormalities were associated with ELX/TEZ/IVA treatment, and were common causes of treatment interruption and occasional causes of treatment discontinuation.

### Benefits/harms

6.20 A benefits and harms table is not presented as the submission did not present comparative data to allow for a quantitative comparison of the benefits and harms of ELX/TEZ/IVA, TEZ/IVA, IVA or BSC.

### Clinical claim

6.21 The submission described ELX/TEZ/IVA as:

- superior in terms of effectiveness compared with IVA plus BSC in patients with mutations responsive to both IVA and ELX/TEZ/IVA,

- superior in terms of effectiveness compared with TEZ/IVA plus BSC in patients with TEZ/IVA-eligible residual function and non-canonical splice mutations,
  - superior in terms of effectiveness compared with BSC in patients with all other mutations.
- 6.22 The evaluation considered this claim was not adequately supported. There was no systematic analysis presented of any comparative data or data for patients switching between treatments to determine whether ELX/TEZ/IVA was superior to either IVA or TEZ/IVA. The data presented suggested that patients who switched to ELX/TEZ/IVA from another CFTRm, in most cases IVA, obtained minimal additional benefit. It is possible that for some mutations not otherwise eligible for treatment with a CFTR modulator ELX/TEZ/IVA may be effective but there was no evidence that it is the case for all other mutations and for some mutations the balance of evidence suggested that ELX/TEZ/IVA is not effective.
- 6.23 The submission described ELX/TEZ/IVA as comparable in terms of safety to IVA plus BSC, TEZ/IVA plus BSC and BSC alone. This claim was not adequately supported as there were no data to compare the safety of the ELX/TEZ/IVA with TEZ/IVA or IVA alone, and ELX/TEZ/IVA was inferior with respect to BSC in terms of safety.
- 6.24 The PBAC considered the claim of superior comparative effectiveness versus IVA plus BSC and TEZ/IVA plus BSC was not supported by the data. The PBAC considered that the claim of superior comparative effectiveness versus BSC was uncertain but, overall, was likely to be reasonable.
- 6.25 The PBAC considered the claim of comparable safety compared to IVA, TEZ/IVA and BSC was not supported by the data.

### **Economic analysis**

- 6.26 The submission did not present an economic analysis. The submission stated that this approach was the same as that considered by the PBAC meeting in Nov 2023, for the submission for patients with one of 92 mutations responsive to IVA potentiation based on clinical or in-vitro data. The submission stated that based on the PBAC consideration that 'ivacaftor was likely to be cost-effective' if the unit price was no higher than the unit price of ELX/TEZ/IVA, the same approach could be accepted for the current application for patients with non-*F508del* ELX/TEZ/IVA responsive mutations.
- 6.27 The submissions requested the price of ELX/TEZ/IVA for the non-*F508del* ELX/TEZ/IVA responsive patients being the same as the current effective price for the *F508del* mutation group.

## Drug cost/patient/year

Table 10: Drug cost per patient for proposed and comparator drugs used in financial estimates

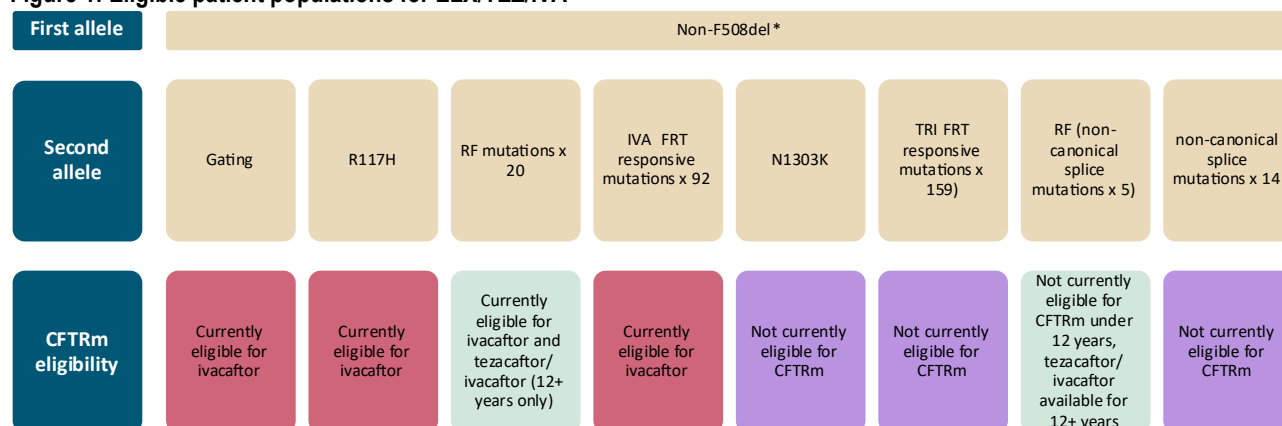
	ELX/TEZ/IVA	TEZ/IVA	IVA (gating)	IVA (non-gating)
AEMP per pack/28day supply (A)	\$█	\$█	\$█	\$█
Compliance (B)	90%	80%	80%	90%
Cost/patient/year ((365.25/28)pack/year*A*B)	\$█	\$█	\$█	\$█

Source: Calculated during the evaluation.

## Estimated PBS usage & financial implications

- 6.28 This submission was not considered by DUSC. A utilisation review of ELX/TEZ/IVA is planned<sup>2</sup>.
- 6.29 The submission stated that the approach to estimating the usage and financial implications for listing ELX/TEZ/IVA for the new proposed populations was the same as that previously accepted by the PBAC in other submissions for CFTRm drugs. The approach was a mix of epidemiological estimates for the currently untreated populations and estimates of switching from currently treated patient groups, based on age and mutation. The populations as identified in the submission are shown in Figure 1.

Figure 1: Eligible patient populations for ELX/TEZ/IVA



Source: Figure 4.1, p117 of the submission. CFTRm, Cystic fibrosis transmembrane conductance regulator; IVA, ivacaftor; RF, residual function; TRI, TRIKAFTA

\*Non-F508del includes any mutation that is not F508del including those mutations listed for Second Allele

- 6.30 The potential population eligible for ELX/TEZ/IVA under the requested restriction was estimated from data sourced from the Australian Cystic Fibrosis Data Registry. A ‘bespoke’ analysis was carried out, using the 2023 CF population data stratified by age and genotype.

<sup>2</sup> <https://www.pbs.gov.au/industry/listing/elements/dusc-meetings/dos/2024/DUSC-Outcome-Statement-October-2024.pdf>

**Table 11: Key inputs for financial estimates**

Parameter	Source	Estimate	Comment
Number of people with CF in Australia in 2022 (% of total)	ACFDR August 2023 data request	All patients ≥ 2 years: 3,671 2 < 6 years: 322 (9%) 6 < 12 years: 515 (14%) 12+: 2,834 (77%)	Data source previously accepted by PBAC
Number of net new patients with CF in Australia	ACFDR 2020-2023	65	Based on average of 81 new diagnoses per year less 16 deaths
Uptake rate	Stated to be expected to be high as some patients have been 'warehoused' pending this submission	95% years 1-6	
Switching assumptions	Previous submission methodology ranging from 100% to 60%	From IVA (non-gating): 100% From IVA, gating: 60% From TEZ/IVA: 100%	Based on clinician feedback.
Compliance rate	Same as used in the March 2024 IVA rare submission	90%	May be reasonable
Discontinuation rate	Previous PBAC consideration of ELX/TEZ/IVA and clinical trials	1.4 in Year 1; 4.2% in Year 2	Consistent with previous submissions
Copayment	Assumed 100% of scripts dispensed in public hospital setting	\$13.90	Consistent with previous submission. Assumed no RPBS use.
Grandfathered patients	none		
Effective prices for IVA, TEZ /IVA, ELX/TEZ/IVA	AEMP	IVA nonF/gating: \$ [REDACTED] IVA non F/non G: \$ [REDACTED] TEZ/IVA: \$ [REDACTED] ELX/TEZ/IVA: \$ [REDACTED]	Assumed 100% public hospital use.
MBS items	Liver Functions tests Ophthalmological review	MBS Item 66512, \$17.70 MBS item 104, \$98.50 Expenditure calculated using default [REDACTED] % rebate.	As for previous submissions: LFTs every 3 months for the first year; annually thereafter. 2 ophthalmological visits in the first year of treatment.

Source: Table 4.2 p119, Table 4.20, p130, Table 4.25, p134 and text of Section 4 of the submission. ACFDR=Australian Cystic Fibrosis Data Registry; CF= cystic fibrosis; ELX/TEZ/IVA= elexacaftor/tezacaftor /ivacaftor; IVA=ivacaftor

6.31 The submission estimated the number of patients eligible for ELX/TEZ/IVA by age and mutations, as shown in Table 12.

Table 12: Breakdown of non-F508del 2023 prevalent population eligible for ELX/TEZ/IVA by age and mutation, n (% of age total)

Age group	non-F508del								All eligible for E/T/I(non-F)
	Gating	R117H	RF mutations x 20	IVA responsive in vitro	N1303K	E/T/I responsive mutations	RF (non-canonical splice mutations x 5)	Non-canonical splice mutations x 14	
2 <6 yrs	7 (2.2%)	2 (0.6%)	3 (0.9%)	1 (0.3%)	2 (0.6%)	1 (0.3%)	1 (0.3%)	2 (0.6%)	19 (5.9%)
6 <12 yrs	6 (1.2%)	8 (1.6%)	5 (1.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)	21 (4.1%)
12+	63 (2.2%)	26 (0.9%)	28 (1.0%)	10 (0.4%)	15 (0.5%)	8 (0.3%)	1 (0.0%)	2 (0.1%)	153 (5.4%)
Total 2+ yrs	76 (2.1%)	36 (1.0%)	36 (1.0%)	11 (0.3%)	17 (0.5%)	10 (0.3%)	2 (0.1%)	5 (0.1%)	193 (5.3%)

Source: Table 4.3, p 121 of the submission. E/T/I = elxacaftor/tezacaftor/ivacaftor; FRT= Fischer Rat Thyroid; IVA=ivacaftor; resp = responsive; RF= residual function.

Patients who are currently ineligible for CFTR modulator therapy under existing PBS restrictions are highlighted in blue.

6.32 As in previous submissions, eligible populations were estimated separately according to three groups: those eligible for treatment under the existing Deeds, who will switch to ELX/TEZ/IVA; those ineligible for use under the existing Deeds, and those eligible but currently not on treatment. The populations treated with IVA were considered separately due to the different prices for patients with Gating and non-Gating mutations so there were four different populations in total:

- IVA treated patients with IVA responsive mutation, excluding gating mutations (referred to as ‘non-gating’ in the tables)
- IVA treated patients with gating mutations (referred to as ‘gating’ in the tables)
- Patients eligible for TEZ/IVA
- Patients not currently eligible.

6.33 Based on the number of patients with the specified mutations and those patients expected to switch from existing treatment, the total number of patients was estimated as shown in Table 135.

6.34 It was not clear why patients would switch from existing PBS listed treatment to ELX/TEZ/IVA. Although switch was reported in the observational data, it was not associated with improved outcomes. The Pre-Sub-Committee Response stated that Australian clinicians have consistently highlighted that ELX/TEZ/IVA is the preferred treatment for eligible patients and the reasons for switching to ELX/TEZ/IVA extend beyond outcomes reported in the submission and switching is expected on listing of ELX/TEZ/IVA for the requested indication.

**Table 13: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Number of patients treated</b>						
Currently CFTRm - naïve/ineligible	1	1	1	1	1	1
Switching from IVA – non-gating	1	1	1	1	1	1
Switching from IVA – gating	1	1	1	1	1	1
Switching from TEZ/IVA	1	1	1	1	1	1
TOTAL	1	1	1	1	1	1
Annual initiating population	1	1	1	1	1	1
<b>Number of scripts dispensed<sup>a</sup></b>						
ELX/TEX/IVA	2	2	2	2	2	2
Ivacaftor scripts replaced – non-gating	-2	-2	-2	-2	-2	-2
Ivacaftor scripts replaced - gating	-1	-1	-2	-2	-2	-2
TEZ/IVA scripts replaced	-1	-1	-1	-1	-1	-1
<b>Estimated financial implications of ELX/TEZ/IVA</b>						
Cost to PBS/RPBS less copayments, ELX/TEZ/IVA	3	3	3	3	3	3
<b>Estimated financial implications for ivacaftor and TEZ/IVA</b>						
Cost to PBS/RPBS less copayments – IVA, non gating	4	4	4	4	4	4
Cost to PBS/RPBS less copayments – IVA, gating	4	4	4	4	4	4
Cost to PBS/RPBS less copayments - TEZ/IVA	4	4	4	4	4	4
TOTAL	4	4	4	4	4	4
<b>Net financial implications</b>						
Net cost to PBS/RPBS	5	5	5	5	5	5
Net cost to MBS	5	5	5	5	5	5
Net cost to PBS/RPBS/MBS	5	5	5	5	5	5

Source: Tables 4.5, 4.6, 4.7, 4.13, 4.14, 4.17, 4.26, 4.28, 4.31; of the submission.

<sup>a</sup> Assuming 11.74 scripts per year as estimated by the submission.

The redacted values correspond to the following ranges

1 <500

2 500 to < 5,000

3 \$10 million to < \$20 million

4 net cost saving

5 \$0 to < \$10 million

6.35 The total cost to the PBS/RPBS of listing ELX/TEZ/IVA was estimated to be \$10 million to < \$20 million in Year 6, and a total of \$100 million to < \$200 million in the first 6 years of listing. The net cost to the PBS/PBS accounting for reduced use of other CFTR modulators, was estimated to be \$0 to < \$10 million in Year 6 and a total of \$0 to < \$10 million in the first 6 years of treatment.

6.36 The pre-PBAC response stated the ACM advice will capture approximately <500 more patients per year than estimated in the submission. The PBAC noted the basis for the increased patient population and the number of additional patients was unclear.

## Financial Management – Risk Sharing Arrangements

6.37 The submission proposed that the requested population for ELX/TEZ/IVA in this submission be included in the existing Deed with no change to the subsidisation caps.

6.38 Information for the shared CF cap is provided in Table 14. Ivacaftor was included in the shared cap in June 2024.

Table 14: Current RSA for IVA, LUM/IVA, TEZ/IVA and ELX/TEZ/IVA (█% rebate for expenditure over the cap)

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

Source: Department of Health

ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; IVA = ivacaftor; LUM/IVA = lumacaftor/ivacaftor; TEZ/IVA = tezacaftor/ivacaftor

Note: Year 3 contains 10 months of data only and the draft amounts may change subject to end of financial year adjustments █

## 7 PBAC Outcome

7.1 The PBAC recommended that the listing of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) for the treatment of cystic fibrosis (CF) be extended to include patients who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to ELX/TEZ/IVA based on clinical and/or *in vitro* assay data. The PBAC noted the clinical benefit was uncertain but it was reasonable for ELX/TEZ/IVA to be available for this population, some of whom do not currently have access to CFTR modulators. The PBAC considered ELX/TEZ/IVA was likely to be cost-effective for this population at the current PBS price, noting that this population should be included in the current risk sharing arrangement for CFTR modulators with no increase in expenditure caps.

7.2 The PBAC acknowledged the consumer comments strongly supported the extension of the listing for ELX/TEZ/IVA.

7.3 The PBAC considered the proposed restriction criteria were appropriate but that some amendments may be required to remove reference to the list of mutations in the TGA approved Product Information (see paragraphs 2.2 and 2.3), depending on the final TGA approval.

7.4 The PBAC advised the listing for the ELX 50 mg/ TEZ 25 mg/ IVA 37.5 mg tablet presentation could be made available for patients aged 2 to 6 years (as requested in

- the pre-PBAC response, see paragraph 3.3). The PBAC noted this would provide young patients and their carers with a choice regarding the most appropriate dosage form.
- 7.5 The PBAC noted the submission nominated IVA + BSC, TEZ/IVA + BSC and BSC alone as comparators, depending on the mutation and age of patients. The PBAC considered the nominated comparators were reasonable; however, it would have been informative to compare commencing treatment with ELX/TEV/IVA at 2 years with commencing treatment with TEZ/IVA at 12 years of age for some populations. The PBAC noted there was no comparative evidence versus IVA or TEZ/IVA in the relevant populations presented.
- 7.6 The PBAC noted the submission presented data from a number of data sources (see Table 4) to support the clinical claim that ELX/ TEZ/IVA has superior effectiveness versus the nominated comparators. Overall, the PBAC noted ELX/TEZ/IVA treatment was associated with decreases in sweat chloride and increases in ppFEV<sub>1</sub>. The PBAC noted there was a wide variation in response across the different mutations and limited information for some mutations; however, the PBAC acknowledged the challenges associated with conducting clinical trials in patients with rare mutations. The PBAC considered that, overall, treatment with ELX/TEZ/IVA was likely to provide a clinical benefit in the requested populations; however, the magnitude of the benefit was uncertain.
- 7.7 The PBAC considered the claim that ELX/TEZ/IVA had comparable safety to the nominated comparators was not supported by data presented. However, the PBAC noted the incidence and type of adverse events were similar to that observed in other populations.
- 7.8 The PBAC noted no economic evaluation was presented, with the sponsor requesting ELX/TEZ/IVA be made available for this population at the same price as it is currently reimbursed through the PBS on the basis of equity of access for patients with very rare mutations. The PBAC recalled it had initially recommended the listing of CFTR modulators with high and likely underestimated incremental cost effectiveness ratios on the basis of high clinical need. The PBAC noted that, over time, expanded populations (i.e., for younger patients and those with rarer mutations) have been recommended for listing. The PBAC noted the magnitude of clinical benefit is less certain in the expanded populations, and this may result in use that is less cost effective overall.
- 7.9 The PBAC considered that the methodology for estimating the number of additional patients that would be eligible for ELX/TEZ/IVA and the estimated financial impact was reasonable.
- 7.10 The PBAC advised that the extended population should be included in the existing Risk Sharing Arrangement with no increase in expenditure caps as proposed in the submission (see paragraph 6.37).
- 7.11 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

Specifically, the PBAC found that in the circumstances of its recommendation for ELX/TEZ/IVA:

- a) Based on the available evidence the magnitude of benefit of treatment with ELX/TEZ/IVA was not able to be quantified, and therefore the criteria of having a substantial and clinically relevant improvement in efficacy compared to the nominated comparators was not met;
- b) The treatment is expected to address a high and urgent unmet clinical need for some of the additional population as there are no alternative treatment options;
- c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

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

**Outcome:**

Recommended

## 8 Recommended listing

8.1 Amend existing listing as follows (additions are in italics and deletions are in strikethrough):

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ELEXACAFTOR+TEZACAFTOR+IVACAFTOR (& IVACAFTOR					
Elexacافت 100 mg + tezacافت 50 mg + ivacافت 75 mg granules [28] (& ivacافت 75mg granules [28], 56 sachets	14228W 14280N	1	1	5	Trikafta
Elexacافت 80 mg + tezacافت 40 mg + ivacافت 60 mg granules [28] (& ivacافت 59.5 mg granules [28], 56 sachets	14227T 14279M	1	1	5	Trikafta
Elexacافت 50 mg + tezacافت 25 mg + ivacافت 37.5 mg tablet [56] (& ivacافت 75 mg tablet [28], 84	13276R 13266F	1	1	5	Trikafta
Elexacافت 100 mg + tezacافت 50 mg + ivacافت 75 mg tablet [56] (& ivacافت 150 mg tablet [28], 84	12936W 12938Y	1	1	5	Trikafta
<b>Concept ID</b> (for internal Dept. use)	<b>Category / Program:</b> <input checked="" type="checkbox"/> Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)				
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners				
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (FULL assessment) in writing only via post/HPOS upload)				
	<b>Authority type:</b> <input checked="" type="checkbox"/> Complex Authority Required (CAR)				
Ⓢ	<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.				

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	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
	<p><b>Administrative Advice:</b>            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 <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a>            Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at <a href="http://www.servicesaustralia.gov.au/hpos">www.servicesaustralia.gov.au/hpos</a>            Or mailed to:            Services Australia            Complex Drugs            Reply Paid 9826            HOBART TAS 7001</p>
	<p><b>Administrative Advice:</b>            For the purposes of this restriction, PBS-subsidised 'CFTR modulator' means ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor and elexacaftor/ tezacaftor/ ivacaftor.</p>
	<b>Condition:</b> Cystic fibrosis
	<b>Indication:</b> Cystic fibrosis
<b>Restriction Summary [new1] / Treatment of Concept: [new1A]</b>	
	<b>Treatment Phase:</b> Initial treatment
	<b>Treatment criteria:</b>
	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
	<b>AND</b>
	<b>Treatment criteria:</b>
	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
	<b>AND</b>
	<b>Clinical criteria:</b>
	<del>Patient must have at least one F508del mutation in the cystic fibrosis transmembrane conductance (CFTR) gene</del> Patient must have at least one mutation in the CFTR gene that is responsive to elexacaftor/tezacaftor/ivacaftor potentiation based on clinical and/or in vitro assay data
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must be given concomitantly with standard therapy for this condition
	<b>AND</b>
	<b>Clinical Criteria:</b>
	Patient must have either chronic sinopulmonary disease or gastrointestinal and nutritional abnormalities, prior to initiating treatment with this drug
	<b>Population criteria: <u>(specific to ELX 100mg + TEZ 50mg + IVA 75mg (&amp;) IVA 75mg) – granules</u></b>
	Patient must be 2 to 5 years of age
	<b>Population criteria: <u>(specific to ELX 80mg + TEZ 40mg + IVA 60mg (&amp;) IVA 59.5mg) – granules</u></b>
	Patient must be 2 to 5 years of age
	<b>Population criteria: <u>(specific to ELX 100mg + TEZ 50mg + IVA 75mg (&amp;) IVA 150mg) – tablets</u></b>
	Patient must be at least 6 years of age
	<b>Population criteria: <u>(specific to ELX 50mg + TEZ 25mg + IVA 37.5mg (&amp;) IVA 75mg) – tablets</u></b>
	Patient must be aged between 6 2 and 11 years inclusive

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	<p><b>Prescribing instructions:</b> For the purposes of this restriction, the list of mutations considered to be responsive to elexacaftor/tezacaftor/ivacaftor is defined in the TGA approved Product Information</p>
	<p><b>Prescribing instructions:</b> 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.</p>
	<p><b>Prescribing Instructions:</b> The authority application must be via the Online PBS Authorities System, or in writing and must include: (1) details of the proposed 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.</p>
	<p><b>Prescribing instructions:</b> The authority application must be via the Online PBS Authorities System, or in writing via HPOS form upload or mail and must include: (1) details of the pathology report substantiating the specific mutation considered to be responsive to elexacaftor/tezacaftor/ivacaftor as listed in the TGA approved PI - quote each of the: (i) the specific mutation listed in the TGA approved PI; (ii) name of the pathology report provider, (iii) date of pathology report, (iv) unique identifying number/code that links the pathology result to the individual patient; and (2) current CYP3A4 inhibitors, CYP3A4 inducers and IV antibiotics</p>
	<p><b>Prescribing Instructions:</b> If the application is submitted through HPOS form upload or mail, it must include: (i) details of the proposed prescription; and (ii) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).</p>
<b>Restriction Summary [new2] / Treatment of Concept: [new2A]</b>	
	<b>Treatment Phase:</b> Continuing treatment
	<b>Treatment criteria:</b>
	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
	<b>AND</b>
	<b>Treatment criteria:</b>
	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
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must be given concomitantly with standard therapy for this condition.
	<b>AND</b>
	<b>Population criteria: (specific to ELX 100mg + TEZ 50mg + IVA 75mg (&amp;) IVA 75mg) – granules</b>
	Patient must be 2 to 5 years of age
	<b>Population criteria: (specific to ELX 80mg + TEZ 40mg + IVA 60mg (&amp;) IVA 59.5mg) – granules</b>
	Patient must be 2 to 5 years of age
	<b>Population criteria: (specific to ELX 100mg + TEZ 50mg + IVA 75mg (&amp;) IVA 150mg) – tablets</b>

	Patient must be at least 6 years of age
	<b>Population criteria: <u>(specific to ELX 50mg + TEZ 25mg + IVA 37.5mg (&amp;) IVA 75mg) – tablets</u></b>
	Patient must be aged between 6 2 and 11 years inclusive
	<b>Prescribing instructions:</b> 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.
	<b>Prescribing instructions:</b> The authority application must be <i>via the Online PBS Authorities System, or in writing via HPOS form upload or mail</i> and must include: <del>(1) details of the proposed a completed authority prescription form; and</del> <del>(2) a completed Cystic Fibrosis elexacaftor, tezacaftor with ivacaftor PBS Authority Application Supporting Information Form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice) which includes details of any ; and</del> (3) current CYP3A4 inhibitors, CYP3A4 inducers and IV antibiotics.
	<b>Prescribing Instructions:</b> <i>If the application is submitted through HPOS form upload or mail, it must include:</i> <i>(i) details of the proposed prescription; and</i> <i>(ii) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).</i>

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

## 9 Context for Decision

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

## 10 Sponsor's Comment

Vertex welcomes the recommendation by the Pharmaceutical Benefits Advisory Committee (PBAC), to expand the PBS listing of TRIKAFTA® (elexacaftor/tezacaftor/ivacaftor and ivacaftor) to include people with cystic fibrosis aged 2 years and older with a mutation in the *CFTR* gene that is considered responsive to treatment based on clinical and/or *in vitro* data. This is an important first step to achieving reimbursed access for eligible patients in Australia.