An addendum to this Public Summary Document has been included at the end of the document.

5.03 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   
Trikafta®  
VERTEX PHARMACEUTICALS (AUSTRALIA) PTY. LTD.

1. Purpose of submission
   1. The submission requested a Section 100 (Highly Specialised Drugs Program) Authority Required listing for elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) for the treatment of cystic fibrosis (CF) in patients who are aged 6 to 11 years and who have at least one F508del mutation on the cystic fibrosis transmembrane conductance regulator (CFTR) gene (F/any).
   2. The submission identified six populations (aged 6 to 11 years old) who would be eligible for treatment with ELX/TEZ/IVA: (1) patients who are homozygous for F508del in the CFTR gene (F/F); (2) patients who are heterozygous for F508del in the CFTR gene with a residual function mutation (F/RF); (3) patients who are heterozygous for F508del in the CFTR gene with a gating mutation (F/G); (4) patients who are heterozygous for F508del in the CFTR gene with a minimal function mutation (F/MF); (5) patients who are heterozygous for F508del in the CFTR gene with a R117H mutation (F/R117H) and (6) patients who are heterozygous for F508del in the CFTR gene with a second mutation that is unknown or not yet characterised as residual function or minimal function (F/not yet characterised).
   3. Listing was requested on the basis of: (1) a cost-effectiveness analysis versus lumacaftor/ivacaftor (LUM/IVA) in the F/F population; (2) a cost-effectiveness analysis versus best supportive care (BSC) in the F/MF population and (3) a cost comparison versus ivacaftor (IVA) in the F/G population. The key components presented in the submission are provided in Table 1.

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

|  |  |
| --- | --- |
| **Component** | **Description** |
| **Population** | CF patients aged 6-11 years who have at least one F508del mutation in the CFTR gene (F/any) |
| **Intervention** | For CF patients 6-11 years inclusive weighing < 30 kg: Two fixed-dose combination tablets containing 50 mg of elexacaftor, 25 mg of tezacaftor and 37.5 mg of ivacaftor in the morning. One tablet containing 75 mg ivacaftor in the evening, approximately 12 hours apart.  For CF patients 6-11 years inclusive weighing ≥ 30 kg: Two fixed-dose combination tablets containing 100 mg of elexacaftor, 50 mg of tezacaftor and 75 mg of ivacaftor in the morning. One tablet containing 150 mg ivacaftor in the evening, approximately 12 hours apart. |
| **Comparator** | Three comparators:   1. BSC for CF patients aged 6 to 11 years inclusive who are heterozygous for F508del in the CFTR gene with a minimal function mutation (F/MF); or with a residual function mutation (F/RF); or with a R117H mutation (F/R117H); or with a mutation not yet characterised as RF or MF (F/not yet characterised) 2. LUM/ IVA plus BSC for CF patients aged 6 to 11 years inclusive who are homozygous for the F508del in the CFTR gene (F/F) 3. IVA plus BSC for CF patients aged 6 to 11 years inclusive who are heterozygous for F508del in the CFTR gene with a gating mutation (F/G) |
| **Outcomes** | Absolute change from baseline in LCI2.5; sweat chloride; CFQ-R Respiratory Domain Score; LCI5.0; ppFEV; nutritional status (BMI, BMI-for-age z-score, weight, weight-for-age z-score, height, height-for-age z-score, stature, stature-for-height).  Safety and tolerability |
| **Clinical Claim** | For CF patients aged 6 to 11 who have at least one F508del mutation in the CFTR gene (F/any), ELX/TEZ/IVA plus BSC is superior in terms of efficacy and comparable in terms of safety compared to the nominated comparators (LUM/IVA plus BSC, IVA plus BSC or BSC alone). |

Source: Table 1.1.1, p29 of the submission.

BMI= body mass index; BSC= best supportive care; CF= cystic fibrosis; CFQ-R= cystic fibrosis questionnaire-revised; CFTR= cystic fibrosis transmembrane conductance regulator; ELX= elexacaftor; F/any= CF patient with at least one F508del mutation in the CFTR gene; F/F= CF patient homozygous for the F508del-CFTR mutation; F/G= CF patient heterozygous for the F508del in the CFTR gene with a gating mutation; F/MF= CF patient heterozygous for the F508del in the CFTR gene with a minimal function mutation; F/not yet characterised= CF patient heterozygous for the F508del in the CFTR gene with a second mutation not yet characterised as minimal function or residual function; F/RF= CF patient heterozygous for the F508del in the CFTR gene with a residual function mutation; IVA= ivacaftor; MF= minimal function; LCI= lung clearance index; LUM= lumacaftor; ppFEV= percent predicted forced expiratory volume; TEZ= tezacaftor; RF= residual function.

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

1. Background

Registration status

* 1. ELX/TEZ/IVA was registered for use in CF patients aged ≥ 6 years who have at least one F508del mutation in the CFTR gene on 1 November 2022.
  2. The TGA Clinical Evaluator stated that cystic fibrosis (CF) does not differ substantially in its clinical characteristics between the paediatric and the adult population and the CFTR gene expresses in the same way for the two populations. Based on this, the TGA Clinical Evaluator considered the open-label single arm study presented (i.e., Study 106[[1]](#footnote-2)) was sufficient to be able to demonstrate efficacy in the paediatric population.

Previous PBAC consideration

* 1. This is the first submission to the PBAC for the 6 to 11 years age group for ELX/TEZ/IVA. Previously, the PBAC recommended ELX/TEZ/IVA for the treatment of CF in patients aged ≥12 years who have at least one F508del mutation in the CFTR gene (F/any) and it was PBS listed from 1 April 2022.
  2. A comparison of the PBS listings and TGA indications for the CFTR directed therapies is presented in Table 2*.*

Table 2**: Comparison of PBS listings and TGA indications for CFTR directed therapies**

|  | **ELX/TEZ/IVA** | **ELX/TEZ/IVA** | **TEZ/IVA** | **LUM/IVA** | **IVA** |
| --- | --- | --- | --- | --- | --- |
| **Date of PBS listinga** | Current submission | 1 April 2022 | 1 December 2019 | 1 October 2018 | 1 December 2014 |
| **Current PBS restriction** | Requested: F/any: 6 to 11 years | F/any: ≥12 years | F/F: ≥12 years  F/RF: ≥12 years  At least one RF: ≥12 years | F/F: ≥2 years | At least one G551D mutation or  at least one Class III mutation: ≥12 months |
| **Current TGA indication** | Supported by TGA Delegate and ACM: For the treatment of CF in patients aged 6 years and older who have at least one F508del mutation in the CFTR gene. | | 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. | For the treatment of CF in patients aged 2 years and older who are homozygous for the F508del mutation in the CFTR gene. | For the treatment of CF in patients aged 4 months and older who have an R117H CFTR mutation or one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R. |

Source: Schedule of Pharmaceutical Benefits (Summary of Changes): 1 April 2022, 1 December 2019; 1 October 2018, 1 December 2018; https://www.pbs.gov.au/pbs/home, https://www.tga.gov.au/resources/artg.

BSC= best supportive care; CF = cystic fibrosis; CFTR = Cystic fibrosis transmembrane conductance regulator; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; F/any = CF patient who have at least one F508del mutation in the CFTR gene; F/F = CF patient homozygous for the F508del-CFTR mutation; F/G = CF patient heterozygous for the F508del in the CFTR gene with a gating mutation; F/MF = CF patient heterozygous for the F508del in the CFTR gene with a minimal function mutation; F/RF = CF patient heterozygous for the F508del in the CFTR gene with a residual function mutation; F/not yet characterised = patients with not yet characterised mutation function; IVA = ivacaftor; TEZ/IVA = tezacaftor and ivacaftor; TGA = Therapeutic Goods Administration.

Note:

a Date represents when the treatment was first listed.

1. Requested listing

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT**  **medicinal product pack** | **Dispensed Price for Max. Qty** | **Max. qty packs** | **Max. qty units** | **№. of**  **Rpts** | **Available brands** |
| Elexacaftor/tezacaftor/ ivacaftor | | | | | |
| Elexacaftor 50 mg/ tezacaftor 25 mg/ ivacaftor 37.5 mg film-coated tablets co-packaged with  ivacaftor 75 mg film-coated tablets | $21,375 published price  $|| effective price | 1 | 84 | 5 | Trikafta, Vertex Pharmaceuticals (Australia) Pty Ltd |
| Elexacaftor 100 mg/ tezacaftor 50 mg/ ivacaftor 75 mg film-coated tablets co-packaged with  ivacaftor 150 mg film-coated tablets | $21,375 published price  $|| effective price | 1 | 84 | 5 | Trikafta, Vertex Pharmaceuticals (Australia) Pty Ltd |

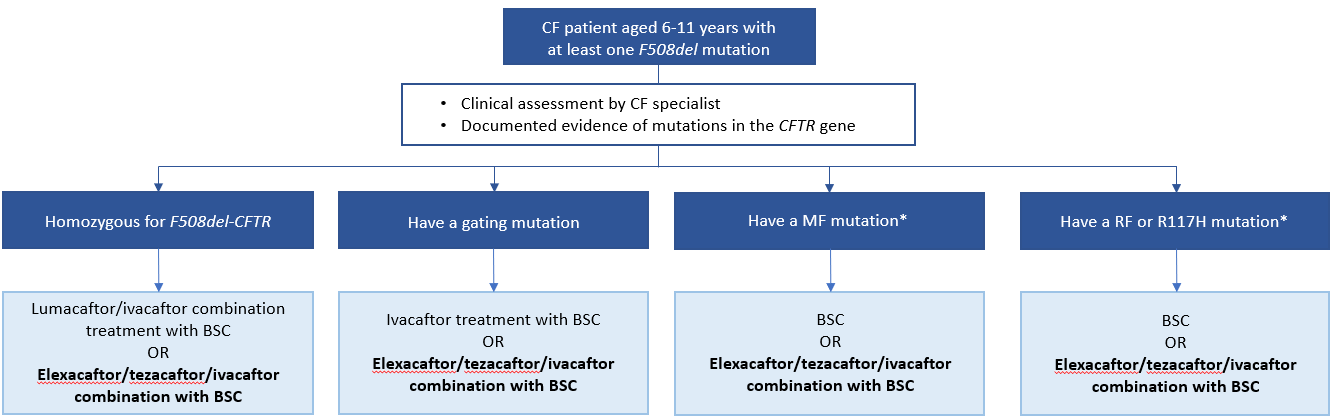
|  |
| --- |
| **Category / Program:** Section 100 – Highly Specialised Drugs Program (Public and Private Hospitals) |
| **Prescriber type:** Dental Medical Practitioners Nurse practitioners Optometrists |
| **Restriction type:**  Authority Required – non-immediate/delayed assessment by Services Australia |
| **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:** |
| Patient must be aged between 6 and 11 years inclusive. |
| **Prescribing Instructions** |
| This pharmaceutical benefit is not PBS-subsidised for this condition in a patient who is currently receiving one of the strong CYP3A4 inducers outlined in the Product Information. |
| 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; 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 |
| 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:** |
| Patient must be aged between 6 and 11 years inclusive. |
| **Prescribing Instructions** |
| This pharmaceutical benefits not PBS-subsidised for this condition in a patient who is currently receiving one of the strong CYP3A4 inducers 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 |

* 1. The PBAC advised the current listing for ELX/TEZ/IVA could be amended to include the population aged 6 to 11 years of age and a new listing could be added for the new, lower strength presentation of ELX/TEZ/IVA for the 6 to 11 years population.

*For more detail on PBAC’s view, see section 7 PBAC outcome*

1. Population and disease
   1. CF is a rare, genetic, systemic disease caused by mutations in the CFTR gene which ultimately leads to defective transport of chloride and other ions. Patients with CF are subject to a progressive loss of lung function, significant excess morbidity and reduced quality of life (QoL), pancreatic insufficiency and gastrointestinal malabsorption, frequent pulmonary exacerbations (PEx) and early death.
   2. The most common mutation in Australia is F508del of the CFTR, present in at least one allele in approximately 90% of CF patients. The F508del mutation leads to an improperly folded CFTR protein and a disruption of the chloride channel opening leading to minimal CFTR chloride transport activity. The submission stated approximately 49% of CF patients aged 6 to 11 years are homozygous for the F508del mutation (F/F); 17% have an F/MF mutation; 7% have an F/G mutation; 5% have an F/RF mutation; 6% have an F/R117H mutation and 16% have an uncharacterised mutation.
   3. ELX/TEZ/IVA is a fixed-dose combination therapy. ELX and TEZ are second-generation CFTR correctors that work by facilitating the cellular processing and trafficking of normal and multiple mutant forms of CFTR, thereby increasing the quantity of functional CFTR protein at the cell surface. IVA is a CFTR potentiator that increases the channel opening probability at the cell surface to enhance chloride transport.
   4. The clinical algorithm provided in the submission (Figure 1) did not consider that once this cohort of patients reaches 12 years of age, they would all be eligible to access ELX/TEZ/IVA as per current PBS listing.

Figure 1: Proposed clinical management algorithm for CF patients who have at least one *F508del-CFTR* mutation



BSC= best supportive care; CF= cystic fibrosis; CFTR= cystic fibrosis transmembrane conductance regulator; MF= minimal function; RF= residual function.

\* F/not yet characterised patients are reallocated 80% to the F/MF population and 20% to the F/RF population as accepted by the PBAC in the 12+ population (ELX/TEZ/IVA May 2021 PBAC Meeting).

1. Comparator
   1. The submission nominated three therapies as the main comparator across the six subpopulations:
2. LUM/IVA for the F/F population;
3. IVA monotherapy for the F/G population and
4. BSC for the F/MF, F/RF, F/R117H and F/not yet characterised populations.
   1. Overall, the evaluation considered the nominated comparators were reasonable, but they do not reflect the longer-term Australian setting where all patients will be eligible for ELX/TEZ/IVA once they turn 12 years. The submission did not compare the proposed listing (commencing treatment between the ages of 6-11 years) with the current listing (commencing treatment after 12 years of age).
   2. The pre-subcommittee response (PSCR) stated that while the sponsor understands the theoretical underpinnings of this marginal analysis approach, such an analysis would require a higher evidentiary burden than previous submissions for younger age groups. The PSCR stated that this approach would require evidence of starting therapy at different ages on very long-term outcomes; such evidence will never be available from clinical trials and registry-based evidence will only be available in decades to come (assuming it could be de-coupled from confounding factors). The ESC noted the PBAC recommended LUM/IVA for patients aged 6 to 11 years (i) at the same cost per patient as the over 12 year population (ii) with a much smaller incremental cost to the PBS and (iii) with a Managed Access Program to demonstrate the clinical benefit.
   3. The ESC considered the appropriate comparator is LUM/IVA (in the F/F population), IVA monotherapy (in the F/G population) or BSC (in the remaining population), followed by ELX/TEZ/IVA from 12 years of age.
5. Consideration of the evidence

Sponsor hearing

* 1. The sponsor requested a hearing for this item. The clinician stated the clinical benefit of ELX/TEZ/IVA was now well established in adults and the benefit could be extended to younger patients. The clinician highlighted the importance of preserving lung function and preventing pulmonary exacerbations in CF patients from a young age.

Consumer comments

* 1. The PBAC noted and welcomed the input from individuals (273), health care professionals (4) and organisations (3) via the Consumer Comments facility on the PBS website. Many comments were received from parents and caregivers outlining the potential benefits of ELX/TEZ/IVA treatment in individuals with CF, including improved life expectancy, a reduction in the need for lung transplants and hospital visits (including associated travel costs), improved quality of life, and allowing an overall sense of normalcy. Some comments noted the improved efficacy and safety of ELX/TEZ/IVA over current treatment options, and noted for some patients, this was the only treatment available. Many comments noted the need for access in the younger population who they considered would benefit from earlier access to ELX/TEZ/IVA due to its ability to reduce organ damage.
  2. The PBAC noted the input received from health professionals outlined the improvement in symptoms in CF patients undergoing ELX/TEZ/IVA treatment. One comment described how the medicine appeared to protect those with milder disease from rapid progression of their disease, but outlined the need for monitoring patients for liver dysfunction and side effects in the eyes in children. Other comments noted that ELX/TEZ/IVA is not a modulator for all genetic mutations and not all patients tolerate it.
  3. The PBAC noted the contributions from three organisations and groups, Cystic Fibrosis Australia, YesToTrikafta (an online community advocacy group) and the National Paediatric Medicines Forum. They were strongly supportive of making ELX/TEZ/IVA available for younger patients with CF on the grounds of effectiveness in comparison with other treatment, lower burden of care for individuals, their families and the hospital system, equity in comparison with other countries and between age groups within Australia, quality of life and the potential prevention of irreversible lung damage prior to the current starting age of 12.

Clinical trials

* 1. The submission was based on the following key trials (in patients 6 to 11 years of age):
* One randomised controlled trial (RCT) comparing ELX/TEZ/IVA to placebo in F/MF patients (Study 116; N = 121);
* One single arm study of ELX/TEZ/IVA in F/F and F/MF patients (Study 106; N = 66) and its corresponding extension (Study 107; N=64);
* One RCT comparing LUM/IVA to placebo in F/F patients (Study 109; N = 204)
* One single arm study of LUM/IVA in F/F patients (Study 011 Part B; N = 58).
  1. Details of the trials presented in the submission are provided in Table 3.

Table 3**: Trials and associated reports presented in the submission**

| **Trial ID** | **Protocol title/ Publication title** | **Publication citation** |
| --- | --- | --- |
| Study 116  VX19-445-116 NCT04353817 | A Study Evaluating Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Subjects 6 Through 11 Years of Age With Cystic Fibrosis and F/MF Genotypes | Clinical Study Report  17 May 2021 |
| Mall, M., et al. (2021). Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Children with Cystic Fibrosis Heterozygous for F508del and a Minimal Function Mutation: A Phase 3b, Randomized, Placebo-Controlled Study. | 24th Deutsche Mukoviszidose-Tagung (DMT) (virtual). |
| Mall MA. Et al (2022), Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 Through 11 Years of Age with Cystic Fibrosis Heterozygous for F508del and a Minimal Function Mutation: A Phase 3B, Randomized, Placebo-Controlled Study. | Am J Respir Crit Care Med 2022; 2022 Dec 1;206(11):1361-1369*.* |
| Study 106  VX18-445-106 NCT03691779 | Clinical Study Report, November 2020: A Phase 3 Study Evaluating the Pharmacokinetics, Safety, and Tolerability of VX-445/TEZ/IVA Triple Combination Therapy in Cystic Fibrosis Subjects 6 Through 11 Years of Age | 7 August 2020 |
| Zemanick, E. T., et al. (2021). A Phase 3 Open-Label Study of ELX/TEZ/IVA in Children 6 Through 11 Years of Age With CF and at Least One F508del Allele. | Am J Respir Crit Care Med 2021; 203(12):1522-1532 |
| Study 107 (rollover from Study 106)  VX19-445-107 NCT04183790 | 24-week Interim Analysis, June 2021: A Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of VX-445/TEZ/IVA Combination Therapy in Subjects With Cystic Fibrosis Who Are 6 Years of Age and Older | 30 April 2021 |
| Ratjen, F, *et al.* (2021). Elexacaftor/tezacaftor/ivacaftor in children aged 6 and older with cystic fibrosis and at least 1 *F508del* allele: Interim results from a Phase 3 open-label extension study. | Journal of Cystic Fibrosis 2021; 20S2: S265 |
| **Studies identified to support the indirect treatment comparison against LUM/IVA** | | |
| Study 109  VX14-809-109 | Ratjen, F, et al. (2017). Efficacy and safety of lumacaftor and ivacaftor in patients aged 6–11 years with cystic fibrosis homozygous for  F508del-CFTR: a randomised, placebo-controlled, phase 3 trial. | Lancet Respir Med 2017;  5(7):557–67 |
| Study 011 Part B  VX13-809-011 | Milla C, et al. (2017). Lumacaftor/Ivacaftor in Patients Aged 6–11 Years with Cystic Fibrosis and Homozygous for F508del-CFTR. | Am J Respir Crit Care Med 2017; 195(7):912–920 |

Source: Compiled during the evaluation based on Table 2.2.1 p56 and Attachment 2 of the submission.

Note: Study 109 and Study 011 previously considered by the PBAC.

* 1. The key features of the trials are summarised in Table 4. The main limitations identified from the evidence supporting the listing are the following:
* Study 116 was subject to possible confounding due to imbalanced ppFEV1 measurements between the ELX/TEZ/IVA and placebo arms, with a lowerproportion of patients measured in the intervention arm compared to the BSC arm at Week 8 (75% vs 85% respectively) and Week 16 (80% vs 88% respectively).
* Key outcome measures in Study 106 such as ppFEV1, CFQ-R respiratory domain score, and the drug acceptability assessment were not recorded by investigators for the majority of participants beyond Week 12 due to the impact of the COVID-19 pandemic. This made outcomes reported at Week 16 and Week 24 vulnerable to confounding due to missing data. The point estimates for Week 16 and Week 24 were based on measurements recorded by 29 (44%) and 15 (23%) patients, respectively, out of the 66 enrolled in the study. Based on this, the results for Study 106 beyond Week 12, and resulting aggregate of mean results ‘through Week 24’ *may be* considered unreliable. The PSCR stated that home-assessed spirometry was permitted in Study 106 due to the impact of the COVID-19 pandemic. Sensitivity analyses using multiple imputation methods as well as prespecified analyses including home-assessed spirometry and including all clinic assessed spirometry data collected through study completion (including unscheduled visits) showed that the MMRM results for ppFEV1 through Week 24 were consistent with the main analysis. Prespecified analysis of sweat chloride, which is an objective measure of efficacy, including unscheduled visits and of CFQ-RD including clinic and home-assessed data were also consistent with the main analysis presented in the submission.
* Both trials (Study 106 and Study 116) were relatively short (24 weeks) in the context of a chronic therapy.

Table 4: **Key features of included evidence**

| Trial | N | Design/ duration | Risk of bias | Patient population | Outcomes | Use in the economic model |
| --- | --- | --- | --- | --- | --- | --- |
| ELX/TEZ/IVA versus PBO (F/MF) | | | | | | |
| Study 116 | 121 | R, DB, MC  24 weeks | Moderate | 6 to 11 years F/MF, ≥70 ppFEV1 | LCI2.5, ppFEV1, CFQ-R Respiratory Domain, sweat chloride | ppFEV1 |
| **ELX/TEZ/IVA (F/F, F/MF)** | | | | | | |
| Study 106 | 66  (F/F:29  F/MF:37) | OL, MC  24 weeks | High | 6 to 11 years F/F and F/MF, ≥40 ppFEV1 | CFQ-R Respiratory Domain, PEx, BMI, ppFEV1, sweat chloride | ppFEV1, BMI |
| Study 107a | 64 | Extension of Study 106  96 weeks (ongoing) | Not used |
| **LUM/IVA versus PBO (F/F)** | | | | | | |
| Study 109 | 204 | R, DB, MC  24 weeks | Low | 6 to 11 years F/F ≥70 ppFEV1 | LCI2.5, ppFEV1, CFQ-R Respiratory Domain, sweat chloride | ppFEV1 |
| **LUM/IVA (F/F)** | | | | | | |
| Study 011 | 58 | OL, MC  24 weeks | High | 6 to 11 years F/F ≥40 ppFEV1 | LCI2.5,, ppFEV1, CFQ-R Respiratory Domain, | ppFEV1 |

Source: Compiled during the evaluation based on the submission

BMI = body mass index; DB = double blind; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; CFQ-R = Cystic Fibrosis Questionnaire-Revised; F/F = CF patient homozygous for the F508del-CFTR mutation; F/G = CF patient heterozygous for the F508del in the CFTR gene with a gating mutation; F/MF = CF patient heterozygous for the F508del in the CFTR gene with a minimal function mutation; F/RF = CF patient heterozygous for the F508del in the CFTR gene with a residual function mutation; MC = multi-centre; N = total patients; ppFEV1 = percent predicted forced expiratory volume in one second; PEx = pulmonary exacerbation; R = randomised; TEZ/IVA = tezacaftor and ivacaftor

Notes:

aStudy 107 is ongoing and is due for completion by April 2024.

* 1. There may be applicability issues for the study populations when compared to the likely Australian population. Based on 2020 data from the Australian Cystic Fibrosis Data Registry (ACFDR), the majority of Australian patients (74%) aged 6 to 11 years were classified as having a normal lung function (ppFEV1 ≥ 90). The proportion of patients with normal lung function was lower in the clinical trials: 53% in Study 116 and 46% in Study 106. Whether the results from the studies would be generalisable to patients treated in Australia was unclear.

Comparative effectiveness

* 1. A summary of the results of the absolute change from baseline to 24 weeks in ppFEV1 across the studies for the different populations is presented in Table 5.

Table 5: Results of absolute change from baseline in ppFEV1 across the trials through week 24

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Trial ID** | **Sub.** | **Comparison** | **Intervention** | | | **PBO** | | | **LSM difference (95% CI)** |
| **n/N** | **Baseline mean (SD)** | **LSM change (SE)** | **n/N** | **Baseline mean (SD)** | **LSM change (SE)** |
| **Randomised trials** | | | | | | | | | |
| Study 116 | F/MF | ELX/TEZ/IVA vs PBO | 60/121 | 91.4 (13.8) | 9.5 (1.5) | 61/121 | 87.2 (15.8) | -1.5 (1.5) | **11.0 (6.9, 15.1)** |
| Study 109 | F/F | LUM/IVA vs PBO | 103/204 | 88.8 (13.7) | 2.5 (0.9) | 101/204 | 90.7 (10.8) | -0.5 (0.9) | **3.0 (0.5, 5.5)** |
| **Non-randomised single arm studies** | | | | | | | | | |
| Study 106 | F/MF | ELX/TEZ/IVA | 34/37 | 88.8 (17.7) | 9.1 (1.4) | NA | NA | NA | **9.1 (6.3, 11.9)** |
| F/F | 25/29 | 11.2 (2.0) | NA | NA | NA | **11.2 (7.2, 15.2)** |
| Study 011 | F/F | LUM/IVA | 58/58 | 91.4 (13.7) | 2.5 (1.3) | NA | NA | NA | 2.5 (‑0.2, 5.2) |

Source: Table 2.5.3 p84; Table 2.5.5 p87 of the submission; Table 14.2.1.2 Study 107 CSR; Table 6 p10, LUM/IVA (PSD), July 2018; Table 4 p916 Milla et al.

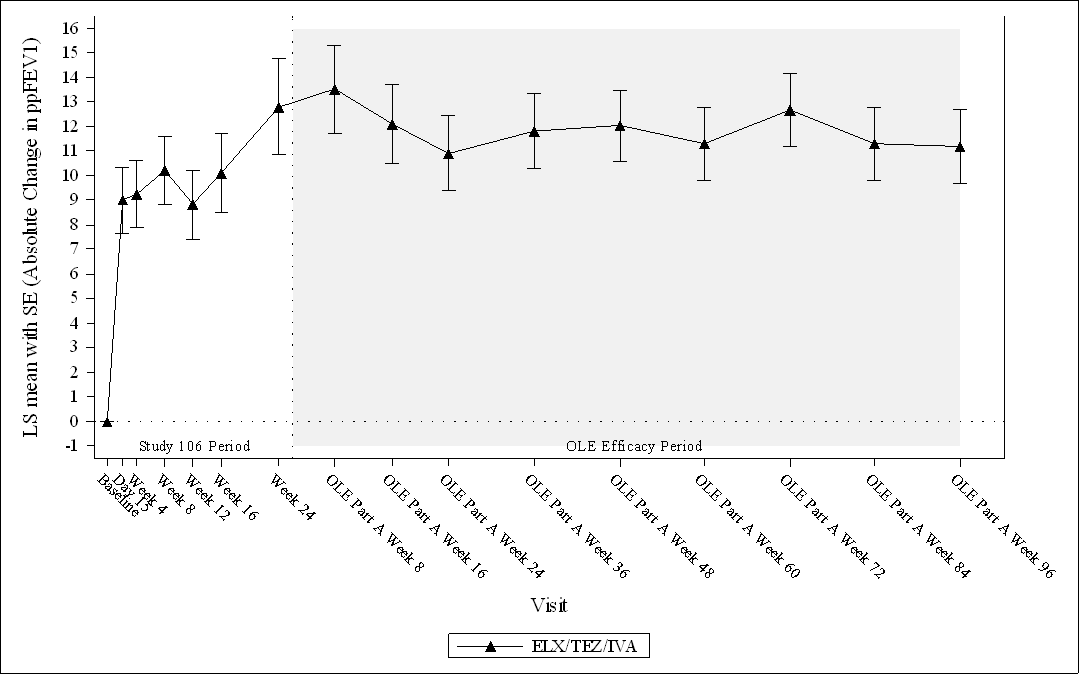
CI = confidence interval; F/F = CF patient homozygous for the F508del-CFTR mutation; F/MF = CF patient heterozygous for the F508del in the CFTR gene with a minimal function mutation; LSM= least square measure; n = number of patients with event; N = total patients in group; PBO= placebo; ppFEV1 = percent predicted forced expiratory volume in one second; SD = standard deviation; SE = standard error; Sub= subpopulation; w = week.

Notes:

Bold indicates statistically significant results

* 1. The improvement in ppFEV1 in Study 116 in F/MF patients (11.0%, 95% CI: 6.9%, 15.1%) exceeded the minimum clinically important difference (MCID) of an absolute change of 10% previously considered appropriate by the PBAC (para 6.10, LUM/IVA, PSD, March 2016; Section 12, ivacaftor PSD, July 2013).
  2. The submission presented longer-term results of respiratory function and physical wellbeing from an interim analysis (IA) of the open label study (Study 107) at 48 weeks (extension study for Study 106; N=64), with data at 96 weeks provided in the PSCR. Study 107 showed a decline in ppFEV1 between Week 24 and Week 48 of 0.7 percentage points (see Figure 2). The mean change from baseline in ppFEV1 from Study 107 at Week 96 was 11.2% (95% CI: 8.3, 14.2).

Figure 2: Study 107 in F/MF and F/F patients: absolute change from parent study 106 baseline in ppFEV1 by visit up to extended Week *96* FAS (provided in PSCR)



Source: provided with PSCR

ELX/TEZ/IVA=elexacaftor/tezacaftor/ivacaftor; FAS=Full Analysis Set; LS=least squares; OLE=open-label extension; ppFEV1= percent predicted forced expiratory volume over 1 second; SE=standard error.

Note: The y-axis corresponds to the LS means from the MMRM models at the IA.

* 1. A summary of the results of the absolute change from baseline to 24 weeks in LCI2.5 across the trials is presented in Table 6.

Table 6: Results of absolute change from baseline in LCI2.5 across the trials, Week 24

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Trial ID** | **Sub.** | **Comparison** | **Intervention** | | | **PBO** | | | **LSM difference (95% CI)** |
| **n/N** | **Baseline mean (SD)** | **LSM change (SE)** | **n/N** | **Baseline mean (SD)** | **LSM change (SE)** |
| **Randomised trials** | | | | | | | | | |
| Study 116 | F/MF | ELX/TEZ/IVA vs PBO | 60/121 | 10.26 (2.22) | -2.29 (0.16) | 61/121 | 9.75 (1.95) | -0.02 (0.16) | **-2.26 (‑2.71,‑1.81)** |
| Study 109 | F/F | LUM/IVA vs PBO | 103/204 | 10.30 (2.36) | -1.01 (0.13) | 101/204 | 10.26 (2.24) | 0.08 (0.13) | **-1.09 (‑1.43, ‑0.75)** |
| **Non-randomised, single arm studies** | | | | | | | | | |
| Study 106 | F/MF | ELX/TEZ/IVA | 27/37 | NR | NR | NA | NA | NA | **-1.72 (‑2.11, ‑1.33)** |
| F/F | 23/29 | NR | NR | NA | NA | NA | **-1.64 (‑2.34, ‑0.94)** |
| Study 011 | F/F | LUM/IVA | 30/58 | 9.99 (2.67) | NR | NR | NR | NR | **‑0.88 (‑1.40, ‑0.37)** |

Source: Table 2.5.1 p824; Table 2.5.5 p87 of the submission; Table 5 p9, LUM/IVA PSD, July 2018; Table 4 p916, Milla et al 2017.

CI = confidence interval; ELX/TEZ/IVA=elexacaftor/tezacaftor/ivacaftor; F/F = CF patient homozygous for the F508del-CFTR mutation; F/MF = CF patient heterozygous for the F508del in the CFTR gene with a minimal function mutation; LSM= least square measure; LUM/IVA= lumacaftor/ivacaftor; n = number of patients with event; N = total patients in group; NR= not reported; PBO= placebo; SD = standard deviation; SE = standard error; w = week

Notes: Bold indicates statistically significant results

* 1. There is no established, externally validated, MCID for LCI. Furthermore, it is uncertain how an improvement in LCI2.5 affects survival (para 6.15, LUM/IVA Public Summary Document (PSD), July 2018). LCI2.5 was not a primary outcome in the submission for CF patients ≥12 years and was not used in the economic model in the current submission*.*
  2. A summary of the absolute change from baseline to 24 weeks in the CFQ-R Respiratory Domain results across the trials is presented in Table 7.

Table 7: Results of absolute change from baseline in CFQ-R Respiratory Domain score across the trials, through 24 weeks

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Trial ID** | **Sub.** | **Comparison** | **Intervention** | | | **PBO** | | | **LSM difference (95% CI)** |
| **n/N** | **Baseline mean (SD)** | **LSM change (SE)** | **n/N** | **Baseline mean (SD)** | **LSM change (SE)** |
| **Randomised trials** | | | | | | | | | |
| Study 116 | F/MF | ELX/TEZ/IVA vs PBO | 60/121 | 85.7 (11.7) | 5.9 (1.6) | 61/121 | 82.7 (14.1) | 0.5 (1.6) | **5.5 (1.0, 10.0)** |
| Study 109 | F/F | LUM/IVA vs PBO | 103/204 | 78.7 (14.0) | 5.5 (1.0) | 101/204 | 77.1 (15.5) | 3.0 (1.0) | 2.5 (-0.1, 5.1) |
| **Non-randomised trials** | | | | | | | | | |
| Study 106 | F/MF | ELX/TEZ/IVA | 37/37 | NR | NR | NA | NA | NA | **6.9 (3.2, 10.6)** |
| F/F | 28/29 | NR | NR | NA | NA | NA | **7.0 (3.9, 10.1)** |
| Study 011 | F/F | LUM/IVA | 58/58 | 78.3 (14.9) | NR | NR | NA | NA | **5.4 (1.4, 9.4)** |

Source: Table 2.5.4 p85, Table 2.5.5 p87 of the submission; Table 2.5.4 of the LUM/IVA Commentary, July 2018; Table 4 p916 Milla et al

CFQ-R = Cystic Fibrosis Questionnaire-Revised; CI = confidence interval; ELX/TEZ/IVA=elexacaftor/tezacaftor/ivacaftor; F/F = CF patient homozygous for the F508del-CFTR mutation; F/MF = CF patient heterozygous for the F508del in the CFTR gene with a minimal function mutation; LSM = least square measure; LUM/IVA= lumacaftor/ivacaftor; n = number of patients with event; N = total patients in group; NA = not applicable; NR= not reported; PBO = placebo; SD = standard deviation; SE = standard error; w = week.

Notes: Bold indicates statistically significant results

* 1. The improvement in CFQ-R with ELX/TEZ/IVA in the F/MF population exceeded the MCID nominated by the submission of an absolute change of 4.0 points. The MCID for CFQ-R has not been previously considered by the PBAC.
  2. A summary of the absolute change from baseline to week 24 in sweat chloride across the trials is presented in Table 8.

Table 8: Results of absolute change from baseline in sweat chloride across the trials through week 24

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Trial ID** | **Sub.** | **Comparison** | **Intervention** | | | **PBO** | | | | **LSM difference (95% CI)** |
| **n/N** | **Baseline mean (SD)** | **LSM change (SE)** | **n/N** | **Baseline mean (SD)** | **LSM change (SE)** |  | |
| **Randomised trials** | | | | | | | | | | |
| Study 116 | F/MF | ELX/TEZ/IVA vs PBO | 60/121 | 102.8 (10.0) | -52.1 (1.5) | 61/121 | 102.6 (8.6) | -0.9 (1.5) | **-51.2 (‑55.3, ‑47.1)** | |
| Study 109 | F/F | LUM/IVA vs PBO | 103/204 | 102.6 (10.3) | -21.6 (1.3) | 101/204 | 103.4 (9.8) | 3.2 (1.3) | **-24.9 (‑28.3, ‑21.4)** | |
| **Non-randomised trial** | | | | | | | | | | |
| Study 106 | F/MF | ELX/TEZ/IVA | 34/37 | *104.4 (7.2)* | NR | NA | NA | NA | **-55.1 (‑59.0, ‑51.2)** | |
| F/F | 26/29 | *99.3 (10.8)* | NR | NA | NA | NA | **-70.4 (‑75.6, ‑65.3)** | |

Source: Table 2.5.2 p83; Table 2.5.5 p87 of the submission; Table 14.2.2.7b p307 Study 106 CSR; Table 6 p10, LUM/IVA PSD; Table 2.5.3 of the LUM/IVA Commentary, July 2018:

CI = confidence interval; ELX/TEZ/IVA=elexacaftor/tezacaftor/ivacaftor; F/F = CF patient homozygous for the F508del-CFTR mutation; F/MF = CF patient heterozygous for the F508del in the CFTR gene with a minimal function mutation; LSM= least square measure; LUM/IVA= lumacaftor/ivacaftor; n = number of patients with event; N = total patients in group; NR = not reported; SD = standard deviation; SE = standard error; w = week; Sub = subpopulation

Notes: Bold indicates statistically significant difference

* 1. Only Study 106 reported the improvement in body mass index (BMI) outcomes for ELX/TEZ/IVA. There was a statistically significant improvement in the absolute change in BMI from baseline of 1.02 kg/m2 (95% CI: 0.76, 1.28; P<0.0001) through Week 24, and a further improvement over an additional 24 weeks of follow-up in Study 107 (1.27 kg/m2; 95% CI 0.96, 1.57). The PBAC previously noted that changes in BMI beyond 24 weeks may indicate clinical effectiveness (para 7.6, LUM/IVA PSD, July 2017). However, the improvement in BMI in Study 106 should be interpreted with caution due to substantial reporting bias beyond Week 12 caused by the COVID-19 pandemic.
  2. Only Study 106 reported pulmonary exacerbations (PEx) as an efficacy outcome. The rate of PEx with ELX/TEZ/IVA was 0.12 per year through Week 24 in Study 106, and further decline to 0.07 per year after an additional 24 weeks follow-up in Study 107.
  3. The submission presented an indirect treatment comparison (ITC) using a mixed model repeated measures (MMRM) meta-analysis to support the claim that ELX/TEZ/IVA was superior in terms of efficacy compared to LUM/IVA. The results of the ITC are presented in Table 9.

Table 9: Results of the indirect comparison for the key effectiveness outcomes

|  | ELX/TEZ/IVA  N=29 | PBO  N=101 | LUM/IVA  N=160 | **LSM (95% CI)** |
| --- | --- | --- | --- | --- |
| **Absolute change (95% CI) in ppFEV1 from baseline through 24 weeks** | | | | |
| Study 106 (F/F patients) | 11.7 (8.4, 15.1)a |  |  |  |
| Study 109 & Study 011 Part B (F/F patients) |  | -2.1 (-3.6, -0.6) | 0.2 (-1.0, 1.4) | **2.4 (0.4, 4.3)** |
| ELX/TEZ/IVA versus LUM/IVA | | | | **11.5 (7.9, 15.1)** |
| ELX/TEZ/IVA versus PBO | | | | **13.9 (10.2, 17.6)** |
| **Absolute change (95% CI) in LCI2.5 from baseline through 24 weeks** | | | | |
| Study 106 (F/F patients) | -2.00 (-2.68, -1.33) |  |  |  |
| Study 109 & Study 011 Part B (F/F patients) |  | -0.05 (-0.31, 0.22) | -1.11 (-1.35, -0.88) | **-1.07 (-1.42, -0.71)** |
| ELX/TEZ/IVA versus LUM/IVA | | | | **-0.89 (-1.60, -0.18)** |
| ELX/TEZ/IVA versus PBO | | | | **-1.96 (-2.68, -1.23)** |
| **Absolute change (95% CI) in weight-for-age z-score from baseline at 24 weeks** | | | | |
| Study 106 (F/F patients) | 0.28 (0.18, 0.39) |  |  |  |
| Study 109 & Study 011 Part B (F/F patients) |  | 0.02 (-0.02, 0.07) | 0.09 (0.05, 0.12) | **0.06 (0.01, 0.12)** |
| ELX/TEZ/IVA versus LUM/IVA | | | | **0.20 (0.08, 0.31)** |
| ELX/TEZ/IVA versus PBO | | | | **0.26 (0.14, 0.37)** |
| **Absolute change (95% CI) in BMI-for-age z-score (kg/m2) from baseline at 24 weeks** | | | | |
| Study 106 (F/F patients) | 0.40 (0.25, 0.55) |  |  |  |
| Study 109 & Study 011 Part B (F/F patients) |  | 0.10 (0.05, 0.16) | 0.05 (-0.02, 0.11) | **0.06 (-0.02, 0.14)** |
| ELX/TEZ/IVA versus LUM/IVA | | | | **0.29 (0.13, 0.46)** |
| ELX/TEZ/IVA versus PBO | | | | **0.35 (0.19, 0.52)** |
| **Absolute change (95% CI) from baseline through 24 weeks in CFQ-R RD score** | | | | |
| Study 106 (F/F patients) | 7.8 (4.3, 11.3) |  |  |  |
| Study 109 & Study 011 Part B (F/F patients) |  | 4.6 (3.1, 6.1) | 2.6 (0.6, 4.6) | 2.0 (-0.5, 4.5) |
| ELX/TEZ/IVA versus LUM/IVA | | | | **3.2 (-0.6, 7.0)** |
| ELX/TEZ/IVA versus PBO | | | | **5.2 (1.2, 9.2)** |

Source: Table 2.6.3 p98 of the submission.

BMI, body mass index; CFQ-R RD, cystic fibrosis questionnaire – revised respiratory domain; CI, confidence interval; ELX/TEZ/IVA, elexacaftor/tezacaftor/ivacaftor; GLI, Global Lung Initiative; LCI, lung clearance index; LS, least squares; LSM = least squares mean MMRM, mixed-effects model for repeated measures; LUM/IVA= lumacaftor plus ivacaftor; LSM= least square measures; PBO= placebo; ppFEV1, percent predicted forced expiratory volume over 1 second.

a The ITC report provided with the submission stated that results may differ from those presented in the clinical study reports [i.e., as presented in Table 5] due to methods used in ITC to provide consistency across the included studies (e.g., covariates included in MMRM, method used to normalize ppFEV1).

Notes: Bold indicates statistically significant results.

* 1. Some transitivity issues between the ELX/TEZ/IVA study (Study 106) and the LUM/IVA studies (Study 109 and Study 011) were identified, mainly:
* All patients in Study 011 were enrolled in the US while >30% of patients in Study 109 and Study 106 were from Europe and Australia. There may be differences across jurisdictions in treatment practices for the management of CF that may have impacted the transitivity of the studies.
* Study 109 was conducted from Oct 2013 to Oct 2015 while Study 106 was conducted between Oct 2018 and Aug 2020. This temporal difference may have impacted the underlying management of the disease, although the impact is likely to be relatively small.
* Several differences across the studies for medications used prior to enrolment. In particular, patients in Study 106 had received prior CFTR treatment (48.3%).
  1. Safety endpoints (i.e. PEx, PEx requiring hospitalisation or PEx requiring IV antibiotic therapy) were not included in the ITC presented by the submission due to the limited number of PEx events reported in Study 106.
  2. The submission presented the long-term safety and efficacy results for ELX/TEZ/IVA in patients ≥12 years based on Study 105 at 144 weeks (IA4). The submission stated that these results were consistent with the results from Study 106/107, showing a similar sustained benefit for up to 48 weeks of treatment as measured by ppFEV1, sweat chloride and BMI. The submission claimed that this demonstrated the validity of extrapolating evidence for efficacy of ELX/TEZ/IVA from adult to paediatric patients and strongly suggested validity of extrapolation of data for longer-term sustained benefit beyond 48 weeks. The results of IA4 appeared to be consistent with the results reported in IA3 which were used to support the long-term effect in patients ≥12 years. The clinical relevance of the improvements observed in patients ≥12 years to younger patients with normal lung function remains for PBAC consideration.
  3. A comparison of single treatment arms was conducted during the evaluation to compare the outcomes in patients treated with ELX/TEZ/IVA across the age groups 6 to 11 years and ≥12 years, which was only possible for F/F and F/MF patients. Acknowledging the inherent limitations of a comparison across treatment arms and differences across study design, treatment effect and patient’s pathophysiology across these patient groups, the following may be concluded:
* In patients with an F/F mutation, similar ppFEV1 change from baseline was observed in the 6 to 11 years cohort at 24 weeks follow up in Study 106 (mean change = 11.2) versus the ≥12 years population at 24 weeks (mean change = 11.2, in Study 109[[2]](#footnote-3)).
* In patients with an F/MF mutation, the results of Study 106 in patients 6 to 11 years reported a lower ppFEV1 change from baseline at Week 24 (mean change= 9.1) compared to the results at 24 weeks in patients ≥12 years (mean change = 13.9[[3]](#footnote-4) in Study 102).
* The ESC noted that, while still meeting the MCID of 4 points, the magnitude of benefit for change in CFQ-R Respiratory Domain score at 24 weeks was substantially lower for the younger children (change of 6 – 7 points) compared to those over 12 years of age (change of approximately 17 points).
  1. The submission did not provide any direct evidence for efficacy or safety for ELX/TEZ/IVA in patients aged 6 to 11 years with a F/G, F/RF or F/R117H mutation. Instead, the submission relied on extrapolated evidence from Study 104, which measured efficacy in patients ≥12 years with a F/RF or F/G mutation vs TEZ/IVA (for F/RF population) and IV (for the F/G population). The PSCR maintained that in CFpatients aged 6 to 11 years old, the efficacy of ELX/TEZ/IVA can be extrapolated to all F/any patients including F/RF, F/F and F/R117H based on the well-established link between CFTR gene mutations and CF and PBAC’s previous assessment of ELX/TEZ/IVA in the 12+ F/any population.
  2. The submission presented an analysis that aimed to evaluate the impact of age at IVA initiation among patients ≥6 years with an F/G mutation on pulmonary outcomes, including ppFEV1 and PEx rates, using the United States CF Foundation Patients Registry (US CFFPR) data through 2019. The results of the analysis showed that patients who had initiated IVA between ages 6 to 10 years had a ppFEV1, on average, 6.3 percentage points higher (101.82 %) than patients who initiated IVA between ages 11 to 15 years (96.09%). The clinical significance of the difference in mean ppFEV1 is uncertain.Further, the submission reported that initiation with IVA between the ages of 6 to 10 years versus 11 to 15 was associated with a 50% lower rate of PEx at ages 11 to 15 years. It is uncertain whether the differences reported in the incidence in PEx are due to lung function deterioration because of age or early treatment.
  3. The PBAC previously considered that on the basis of the aetiology of CF and evidence of similar response in patients aged 2 to 5 years compared to older patients, that it was biologically plausible that earlier treatment would confer some benefit to patients, however the magnitude of any incremental benefit in the short term and over the lifetime of the patient was unknown (para 6.22, ivacaftor PSD, November 2016).

Comparative harms

* 1. The TGA CER concluded that the safety profile of ELX/TEZ/IVA in patients 6 to 11 years was favourable with no new safety concerns. It was noted by the TGA clinical evaluator that the main limitation of the evidence (based on Study 106 only) was the absence of long-term safety data.
  2. A summary of the adverse events for ELX/TEZ/IVA versus placebo in Study 116 for F/MF patients is presented in Table 10.

Table 10: Summary of key adverse events in Study 116 F/MF patients, Safety Set

| Category, n (%) | ELX/TEZ/IVA  N=60 | Placebo  N=61 |
| --- | --- | --- |
| Number of AEs (Total) | 212 | 335 |
| Subjects with any AEs | 48 (80.0) | 57 (93.4) |
| Subjects with AEs leading to study drug discontinuation | 1 (1.7) | 0 |
| Subjects with AEs leading to study drug interruption | 7 (11.7) | 0 |
| Subjects with Grade 3/4 AEs | 2 (3.3) | 2 (3.3) |
| Subjects with related AEs | 26 (43.3) | 23 (37.7) |
| Subjects with SAEs | 4 (6.7) | 9 (14..8) |
| Subjects with related SAEs | 1 (1.7) | 1 (1.6) |
| Subjects with AEs leading to death | 0 | 0 |

Source: 2.5.6 p89-90 of the submission.

AE = adverse event; CI = confidence interval; ELX = elexacaftor; IVA = ivacaftor; RD = risk difference; SAE = serious adverse event; TEZ = tezacaftor

Notes: AEs were coded using MedDRA version 21.1. When summarising number of events = a subject with multiple events within a category was counted multiple times in that category. When summarising number and percentage of subjects = a subject with multiple events within a category was counted only once in that category.

Note:

aWhen summarising number of subjects with related SAE, AEs with relationship of related, possibly related, and missing were counted.

* 1. A summary of the adverse events for ELX/TEZ/IVA in Study 107, which reflects the most updated data, for F/MF and F/F patients is presented in Table 11. At the time of the IA for Study 107, 79.7% patients experienced an AEs, all of which were mild or moderate in severity and generally consistent with manifestations of CF. No children discontinued study drug because of AEs in Study 107.

Table 11: Summary of key adverse events in Study 106 F/F and F/MF patients, Safety Set

| Category, n (%) | Study 106 F/F and F/MF |
| --- | --- |
| ELX/TEZ/IVA  N=66 |
| Number of AEs (Total) | 341 |
| Subjects with any AEs | 65 (98.5) |
| Subjects with AEs leading to study drug discontinuation | 1 (1.5) |
| Subjects with AEs leading to study drug interruption | 1 (1.5) |
| Subjects with Grade 3/4 AEs | 1 (1.5) |
| Subjects with related AEsa | 33 (50.0) |
| Subjects with SAEs | 1 (1.5) |
| Subjects with related SAEsa | 0 |
| Subjects with AEs leading to death | 0 |

Source: Table 2.5.8 p92 of the submission, Ratjen et al 2017, Study 107 IA results poster

AE, adverse event; ELX, elexacaftor; IVA, ivacaftor; SAE, serious adverse event; TEZ, tezacaftor

Notes: AEs were coded using MedDRA version 21.1. When summarising number of events, a subject with multiple events within a category was counted multiple times in that category. When summarising number and percentage of subjects, a subject with multiple events within a category was counted only once in that category.

* 1. The safety data indicated that ELX/TEZ/IVA appeared to be generally well tolerated in the CF population aged 6 to 11 years of age.

Benefits/harms

* 1. A summary of the comparative benefits and harms for ELX/TEZ/IVA versus placebo for the F/MF population and versus LUM/IVA for the F/F population is presented in Table 12.

Table 12: Summary of comparative benefits and harms for ELX/TEZ/IVA versus comparators

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Benefits: Change from baseline at week 24 in absolute change in ppFEV1,** | | | | | | | | | |
| **F/MF** | ELX/TEZ/IVA | | | PBO | | | | Mean difference (95% CI) | |
| N | Mean change | SE | N | Mean change | SE | |
| Study 116, 24 weeks | 60 | 9.5 | 1.5 | 61 | ‑1.5 | -1.5 | | **11.0 (6.9, 15.1)** | |
|  | **ELX/TEZ/IVA** | | | **LUM/IVA** | | | | **Mean difference (95% CI)** | |
| F/F | **N** | **Mean change** | **SE** | **N** | **Mean change** | **SE** | |
| ITC from Study 106/109/011, 24 weeks | 29 | 11.7 | 1.7 | 160 | *0.2* | *0.6* | | **11.5 (7.9, 15.1)** | |
| **Harms** | | | | | | | | | |
| F/MF | ELX/TEZ/IVA  N=60 | PBO  N=61 | RR  (95% CI) | | Event rate/100 patients | | | | RD  (95% CI) |
| ELX/TEZ/IVA | | Comparators | |
| **Patients with Grade 3 or Grade 4 AE** | | | | | | | | | |
| Study 116 | 2 | 2 | 1.02 (0.15, 6.99) | | 3 | | 3 | | 0.00 (-0.05, 0.05) |
| Related AE | | | | | | | | | |
| Study 116 | 26 | 23 | 1.15 (0.75, 1.77) | | 43 | | 38 | | 0.05 (-0.09, 0.19) |
| Patients with any AE | | | | | | | | | |
| Study 116 | 48 | 57 | 0.86 (0.74, 0.99) | | 80 | | 93 | | -0.13 (-0.22, -0.04) |

Source: Developed during the evaluation based on *Table 2.5.3 p84, Table 2.5.6 p89-90; Table 2.6.3 p97-98 of the submission; Table 3.1, “Section 2\_Vertex DOF 10393 – ELX TEZ IVA vs LUM IVA.pdf” provided with the submission.*

AE = adverse event; CI = confidence interval; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; F/F = CF patient homozygous for the F508del-CFTR mutation; F/MF = CF patient heterozygous for the F508del in the CFTR gene with a minimal function mutation; ITC= indirect treatment comparison; PBO= placebo; ppFEV1= percent predicted forced expiratory volume in 1 second; RD = risk difference; RR = relative risk; SE = standard error

Note: Bold indicates statistical significance;

* 1. On the basis of direct evidence from Study 116 presented in the submission, F/MF patients treated with ELX/TEZ/IVA achieved an 11% percentage point increase in the lung capacity (as measured by ppFEV1) compared with placebo at 24 weeks.
  2. On the basis of indirect evidence from Study 106 and Study 109/ 011 presented in the submission, F/F patients treated with ELX/TEZ/IVA achieved a 12% percentage point increase in the lung capacity (as measured by ppFEV1) compared with LUM/IVA at 24 weeks.
  3. On the basis of direct evidence from trials presented in the submission, F/MF patients 6 to 11 years treated with ELX/TEZ/IVA have no increase in the overall likelihood of harms compared with BSC.

Clinical claim

* 1. The submission described ELX/TEZ/IVA as superior in terms of effectiveness and comparable in terms of safety compared with the nominated comparators (LUM/IVA for F/F population, IVA for F/G population and BSC for F/MF, F/RF and F/R117H population). Overall, the ESC considered the therapeutic conclusion presented in the submission was adequately supported by the evidence presented for the F/F and F/MF populations, but the magnitude of benefit in the Australian population of CF patients aged 6 to 11 years of age is uncertain. The main limitations of the clinical evidence are:
* The reliability of the evidence from a single arm study (Study 106) to inform the evidence for the ELX/TEZ/IVA in the F/F population, which may be impacted by the large proportion of patients that missed their clinical assessment visits from Week 12 onwards (>50%).
* The submission used 2-year follow-up data from Study 105 to support the long-term maintained benefit of ELX/TEZ/IVA. However, this evidence was derived from a cohort of patients (mean age of 26.4 years and mean baseline ppFEV1 of 61%) which is not representative of the proposed target population.
  1. The claim of comparable safety appeared to be adequately supported for the F/MF and F/F populations, noting the short duration of follow-up. No critical concerns regarding the safety profile for the proposed registered indication were raised by the TGA.
  2. The submission did not present evidence for the F/RF, F/G or F/R117H populations aged 6 to 11 years. The submission assumed that the results of Study 104, that included patients ≥12 years with an F/RF and F/G mutation are directly applicable to patients aged 6 through 11. The ESC considered the claim of superior efficacy and comparable safety was not adequately supported for the F/RF, F/G and F/R117H patients as the submission did not present direct clinical evidence in patients 6 to 11 years.
  3. The PBAC agreed with the ESC that, on balance, it was reasonable to assume that starting treatment with ELX/TEZ/IVA between the ages of 6 and 11 years old was likely to result in improved outcomes compared to starting it over the age of 12 years old but the magnitude of any benefit remained highly uncertain.
  4. The PBAC noted the lack of clinical evidence for some populations but considered that, on balance, the claim of superior comparative effectiveness:
* vs best supportive care was reasonable for the F/MF population and was likely to be reasonable for the F/RF and F/R117H population.
* vs LUM/IVA was likely to be reasonable for the F/F population
* vs IVA was uncertain for the F/G population, but ELX/ TEZ/ IVA was likely to be superior to best supportive care in this population.
  1. The PBAC considered that the claim of comparable safety to the nominated comparators was reasonable.

Economic analysis

* 1. The submission presented a modelled economic evaluation comparing ELX/TEZ/IVA with LUM/IVA for the F/F population aged 6 to 11 years and comparing ELX/TEZ/IVA with BSC for the F/MF population aged 6 to 11 years. The model structure was similar to that presented in previous CFTR submissions to the PBAC (e.g. LUM/IVA PSD, July 2019, ELX/TEZ/IVA PSD, March 2021). Given the lack of clinical evidence in the F/G, F/R117H and F/RF populations, no economic model was presented to assess the cost-effectiveness in these subgroups.A summary of the key components of the economic evaluation is presented in Table 13.

Table 13**: Key components of the economic evaluation**

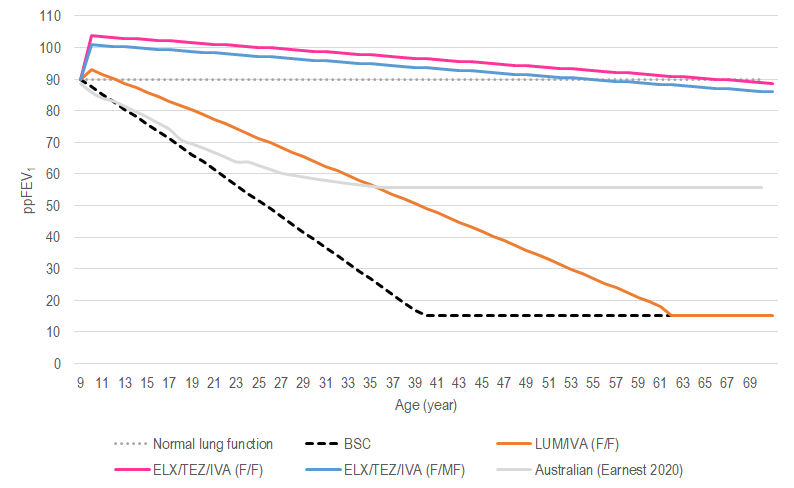
| Component | Description |
| --- | --- |
| Type of analysis | F/F, F/MF: Cost-utility analysis  Combined population with weight of 62% for F/F and 38% for F/MF |
| F/G, F/RF, F/R117: no economic evaluation presented |
| Comparators | LUM/IVA for F/F and BSC for F/MF |
| Outcomes | Quality-adjusted life-years (base case) |
| Time horizon | Lifetime; mean age at commencing treatment of 8.6 years |
| Method used to generate results | Microsimulation |
| Cycle length | First two years of analysis: 4-week  From two years onward: 52-week |
| Discounting | 5% for costs and benefits |
| Transition probabilities | Baseline survival: the Irish CF database |
| Baseline ppFEV1 decline: based on longitudinal registry analyses (Konstan 2007: aged 6- 17 years; de Boer 2011: aged ≥18) |
| Relationship of surrogate outcomes and survival: Liou 2001 |
| Effect: acute increase in ppFEV1: ITC for F/F, Study 116 for F/MF |
| Effect: long-term treatment effects (relative rate of reduction in decline in ppFEV1; rROD in ppFEV1): Study 105 for patients aged ≥ 12 years |
| Health utility | ppFEV1 level-based utility (expert opinion), post lung transplantation (Anyanwu 2002) |
| Costs | Effective price of ELX/TEZ/IVA of $|| per pack ($|| per patient per year; 13.04 packs/year) for F/F and F/MF |
| Software | Microsoft Excel using Visual Basic. |

Source: Table 3.1.1, p131 of the submission.

BSC = best supportive care; CF = cystic fibrosis; F/F = CF patient homozygous for the F508del-CFTR mutation; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; F/MF = CF patient heterozygous for the F508del in the CFTR gene with a minimal function mutation; F/RF = CF patient heterozygous for the F508del in the CFTR gene with a residual function mutation; F/R117H = CF patients who are heterozygous for F508del in the CFTR gene with a R117H mutation; ITC = indirect comparison analysis; LUM/IVA = lumacaftor/ivacaftor; ppFEV1 = percent predicted forced expiratory volume in one second; RCT = randomised controlled trial; rROD = relative rate of reduction in decline.

* 1. The submission proposed the use of LUM/IVA and BSC as the relevant comparators for patients with an F/F or F/MF mutation, respectively.Considering the life-time duration in the model, the ESC consideredthese comparisons were inappropriate as they do not reflect current practice in Australia, where treatment with ELX/TEZ/IVA was PBS-listed in April 2022 for all ≥12 years patients with at least one F508del-CFTR mutation (F/any). This results in an overestimation of the incremental benefits of ELX/TEZ/IVA as it was assumed that LUM/IVA and BSC are used for the lifetime of the patients which disregards the benefits derived from the use of ELX/TEZ/IVA once patients turn 12 years of age. The ESC considereda more informative comparison would have been to compare early treatment starting at an age 6 to 11 years versus initiating treatment with ELX/TEZ/IVA at age 12 years.
  2. In the economic model the long-term ppFEV1 with ELX/TEZ/IVA and LUM/IVA is applied as a decline relative to that observed with BSC; this is referred to as the relative rate of decline (rROD). The submission applied a rROD in ppFEV1 of 90% for ELX/TEZ/IVA in both the F/F and F/MF models.This assumption was based on the results from a propensity score matched analysis that included patients ≥12 years (Study 105 IA3) and data from untreated patients from a US registry (CFFPR).The annualised mean rate of change (RoC) in ppFEV1 forELX/TEZ/IVA was +0.39, which indicated no loss of pulmonary function on average over a 2-year period. The submission stated that the positive slope would result in a rROD higher than 100% and hence assuming a 90% rROD was conservative. However, the rROD was applied for the model lifetime whereas the data reflected a maximum of 2-year follow-up. In addition, Study 105 included patients with a mean age of 26.4 years and a mean baseline ppFEV1 of 61%. These patients are not representative of the proposed target population, and it may be unreasonable to assume these results would be extended to younger patients who are in a healthier stage of the disease (i.e. normal lung function).
  3. The projected mean ppFEV1 over the lifetime of a patient whose mean age at treatment initiation was 8.6 years and baseline ppFEV1 was approximately 90%, is presented in Figure 3. The modelled ppFEV1 curves for patients treated with ELX/TEZ/IVA for both F/F and F/MF patients predicted normal lung function (ppFEV1 >90%) throughout the whole lifetime. This prediction was based on results from Study 105 (in patients ≥12 years) that had a duration of follow up of 2 years. For reference, the figure also includes observational data collected from 2008 to 2019 with a median duration of follow-up from birth to last visit of 21.7 years from Australian CF patients (Earnest et al., 2020). These data suggested a plateauing of ppFEV1 which starts at around 30 years of age. It should be noted that these data included patients who were likely to receive CFTR modulator therapy which became available in 2013 (Ivacaftor recommended at the July 2013 PBAC meeting, LUM/IVA recommended at the July 2018 PBAC meeting).

Figure 3: Predicted change in ppFEV1 over lifetime



Source: developed for the Commentary based on ppFEV1 data from the submission; data for Australian were extracted from Figure 1, Earnest et al., 2020

BSC = best supportive care; F/F = CF patient homozygous for the F508del-CFTR mutation; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; F/MF = CF patient heterozygous for the F508del in the CFTR gene with a minimal function mutation; ppFEV1 = percent predicted forced expiratory volume in one second;

Note: mean baseline age of 8.5 years for F/F and of 8.6 years and F/MF; mean baseline ppFEV1 of 89.8 for F/F (+13.9 acute increase) and of 89.9 for F/MF (+11% acute increase); The grey dash line was included as a reference line to reflect the threshold considered ‘normal lung function’ (ppFEV1 of >90%).

* 1. The assumed 90% rROD is higher than the 80% used to model the long-term decline in patients ≥12 years treated with ELX/TEZ/IVA (para 4.10, ELX/TEZ/IVA PSD, December 2021). The pre-PBAC response stated that evidence of the maintained ppFEV1 rROD has strengthened since the ≥12 years ELX/TEZ/IVA PBAC submission, showing even greater maintenance of ppFEV1 over time. However, the pre-PBAC response stated that, while the sponsor believed that the rROD estimate of 90% used in the 6-11 yrs model is accurate (and likely conservative), a base case analysis is presented with a rROD of 80% for ELX/TEZ/IVA (see paragraph 6.60).
  2. The submission used a lifetime horizon in the model which is consistent with that used in previous CFTR submissions (e.g. LUM/IVA PSD, July 2019, ELX/TEZ/IVA PSD, March 2021). While the lifetime time horizon might be justified as CF is a chronic disease requiring a lifetime treatment, the uncertainty regarding the longer-term effectiveness is high due to the extent of follow-up evidence available (up to 120 weeks in Study 107) and substantial extrapolation required.
  3. The modelled survival curves for F/F and F/MF patients aged 6 to 11 years are presented in Figure 4 and Figure 5 (assuming 90% rROD and 80% rROD). For comparative purposes, the modelled survival for patients aged ≥12 years based on the economic model reviewed at the December 2021 PBAC meeting are also presented. The ESC noted the use of a 90% rROD had a significant impact on the modelled survival.
  4. The predicted long-term survival for patients aged 6 to 11 years treated with ELX/TEZ/IVA appeared to be optimistic and highly uncertain given it relied on heavily extrapolated data from Study 105 (>90% of the survival was extrapolated). The model showed a median age of death of 74 and 77 years for F/MF and F/F patients, respectively. Furthermore, approximately 20% of patients remained alive at 91 years which appears optimistic given a similar proportion of the general Australian population would be expected to be alive at 91 years of age.
  5. The modelled increases in life expectancy associated with starting treatment at a younger age are substantial. This partly reflects the higher mean ppFEV1 prior to commencing treatment for patients aged 6-11 years (approximately 90%) compared with patients aged ≥12 years (approximately 60%) and the higher rROD assumed for ppFEV1 in the model for patients aged 6-11 years (90% versus 80%).

Figure 4: Survival curves for F/F population receiving BSC (orange line), LUM/IVA or TEZ/IVA (green line), and ELX/TEZ/IVA (pink line, 80% rROD and blue line, 90% rROD) when starting treatment at 6 to 11 years submission (left) versus when starting treatment aged ≥12 years from the December 2021 submission (right).

|  |  |
| --- | --- |
| Figure 4: Survival curves for F/F population receiving BSC (orange line), LUM/IVA or TEZ/IVA (green line), and ELX/TEZ/IVA (pink line, 80% rROD and blue line, 90% rROD) when starting treatment at 6 to 11 years submission (left) versus when starting treatment aged ≥12 years from the December 2021 submission (right). | Figure 4: Survival curves for F/F population receiving BSC (orange line), LUM/IVA or TEZ/IVA (green line), and ELX/TEZ/IVA (pink line, 80% rROD and blue line, 90% rROD) when starting treatment at 6 to 11 years submission (left) versus when starting treatment aged ≥12 years from the December 2021 submission (right). |

Source: Created for the ESC ADV using data from the 6-11 year economic model and economic model included in the ELX/TEZ/IVA Dec 2021 submission for patients aged ≥12 years

BSC = best supportive care ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; F/F = homozygous for F508del-CFTR mutations, LUM/IVA = lumacaftor/ivacaftor; rROD = relative rate of decline

Figure 5: Survival curves for F/MF population receiving BSC (orange line) and ELX/TEZ/IVA (pink line, 80% rROD and blue line, 90% rROD) when starting treatment at 6 to 11 years submission (left) versus when starting treatment aged ≥12 years from the December 2021 submission (right).

|  |  |
| --- | --- |
| Figure 5: Survival curves for F/MF population receiving BSC (orange line) and ELX/TEZ/IVA (pink line, 80% rROD and blue line, 90% rROD) when starting treatment at 6 to 11 years submission (left) versus when starting treatment aged ≥12 years from the December 2021 submission (right). | Figure 5: Survival curves for F/MF population receiving BSC (orange line) and ELX/TEZ/IVA (pink line, 80% rROD and blue line, 90% rROD) when starting treatment at 6 to 11 years submission (left) versus when starting treatment aged ≥12 years from the December 2021 submission (right). |

Source: Created for the ESC ADV using data from the 6-11 year economic model and economic model included in the ELX/TEZ/IVA Dec 2021 submission for patients aged ≥12 years

BSC = best supportive care; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; F/MF = heterozygous for F508del-CFTR mutation with a second minimal function allele; rROD = relative rate of decline

* 1. A summary of the key drivers of the model is presented in Table 14.

Table 14: **Key drivers of the model**

| Description | Method/Value | Impact  Base case: $||1/QALY gained  (Combined ICER) |
| --- | --- | --- |
| LoE | LoE of || years for ELX/TEZ/IVA and || years for LUM/IVA. At these time points, the drug prices drop by 90%. | High, favours ELX/TEZ/IVA, removing LoE assumptions the ICER increased to $|2/QALY |
| Time horizon | Lifetime in the base case analysis compared to 2 years follow-up in the clinical trials (Study 105) | High, favours ELX/TEZ/IVA; use of *20*-year time horizon increased the ICER to $*|*3/QALY |
| Long-term reduction in decline of ppFEV1 | rROD in ppFEV1 of 90% for ELX/TEZ/IVA compared to 80% in the aged ≥12 years submission. | Moderate, favours ELX/TEZ/IVA; assuming a rROD the same as the aged≥ 12 years (80%) increased the ICER to $|2/QALY |
| Compliance | 90% compliance rate (same as applied in patients ≥12 years) applied in the model compared with those in the trial (Study 106) of 100% in the trial | Moderate, favours ELX/TEZ/IVA, use of the compliance as in the trials increased the ICER to $|||2/QALY |

Source: Developed during the evaluation

BSC = best supportive care; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; ICER = incremental cost-effectiveness ratio; LoE = loss of exclusivity; ppFEV1 = percent predicted forced expiratory volume in one second; QALYs = quality-adjusted life-years.

*The redacted values correspond to the following ranges:*

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

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

*3 $355,000 to < $455,000*

* 1. The results of the economic evaluation for the F/F, F/MF, and combined populations are provided in Table 15. The ICER for the combined population assumed 62% of patients have an F/F mutation and 38% have an F/MF mutation based on data from the ACFDR in patients aged 6 to 11 years.

Table 15: Incremental cost-effectiveness estimates for patients initiating therapy aged 6 to 11 years (discounted)

|  |  |  |  |
| --- | --- | --- | --- |
| F/F | | | |
|  | **ELX/TEZ/IVA** | **LUM/IVA** | Incremental |
| Life Years | 17.33 | 13.30 | 4.03 |
| QALYs | 17.08 | 11.36 | 5.72 |
| Total costs ($) | | | | | | |
| ICER (cost per LYG) | | | |**1** |
| **ICER (cost per QALY gained)** | | | **|2** |
| F/MF | | | |
|  | **ELX/TEZ/IVA** | **BSC** | Incremental |
| Life Years | 17.25 | 11.33 | 5.92 |
| QALYs | 16.80 | 9.14 | 7.66 |
| Total Costs ($) | | | $521,205 | | |
| ICER (cost per LYG) | | | |**1** |
| **ICER (cost per QALY gained)** | | | **|2** |
| Combined (62% for F/F, and 38% for F/MF) | | | |
|  | **ELX/TEZ/IVA** | **LUM/IVA, BSC** | Incremental |
| Life Years | 17.30 | 12.55 | 4.75 |
| QALYs | 16.97 | 10.51 | 6.46 |
| Total Costs ($) | | | | | | |
| ICER (cost per LYG) | | | |**1** |
| **ICER (cost per QALY gained)** | | | **|2** |

Source: Table 4.1.30, p173 of the submission; worksheet ‘Results’ of the Excel model

BSC = best supportive care; 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; pulmonary exacerbation; LUM/IVA = lumacaftor/ivacaftor; QALYs =, quality-adjusted life-years

*The redacted values correspond to the following ranges:*

*1 $155,000 to < $255,000*

*2 $135,000 to < $155,000*

* 1. The base case ICER for ELX/TEZ/IVA was estimated at $135,000 to < $155,000 per QALY gained for the F/F population and $135,000 to < $155,000 per QALY gained for the F/MF population. The combined ICER was $135,000 to < $155,000 per QALY gained.
  2. A summary of key sensitivity analyses is presented in Table 16. The results of the sensitivity analyses suggest that the model was most sensitive to changing the discounting rate, time horizon and removing the loss of exclusivity (LoE) assumption.

Table 16: **Sensitivity analyses**

| Analyses | Patient population | Incremental cost | Incremental QALY | ICER (changed from base case) |
| --- | --- | --- | --- | --- |
| **Base case** | F/F | $| | 5.72 | $|1 |
| F/MF | $| | 7.66 | $|1 |
| Combined | $| | 6.46 | $|1 |
| Costs and benefits 0% (base case 5%) | F/F | $| | 34.72 | $|2 *(-58%)* |
| F/MF | $| | 38.83 | $|2 *(-55%)* |
| Combined | $| | 36.29 | $|2 *(-58%)* |
| Costs and benefits 3.5% (base case 5%) | F/F | $| | 8.97 | $|3 *(-24%)* |
| F/MF | $| | 11.43 | $|3 *(-21%)* |
| Combined | $| | 9.91 | $|3 *(-23%)* |
| LoE removed (base case 90% reduction after || years for ELX/TEZ/IVA, and || for LUM/IVA) | F/F | $| | 5.72 | $　|　4 (+11%) |
| F/MF | $| | 7.66 | $　|　4 (+74%) |
| Combined | $| | 6.46 | $　|　4 (+39%) |
| 20-year time horizon (base case lifetime years) | F/F | $| | 1.86 | $　|　5 (+186%) |
| F/MF | $| | 3.00 | $　|　6 (+126%) |
| Combined | $| | 2.30 | $　|　5 (+156%) |
| Compliance as in the trials of 100% (base case 90%) | F/F | $| | 5.72 | $　|　4 (+12%) |
| F/MF | $| | 7.66 | $　|　4 (+12%) |
| Combined | $| | 6.46 | $　|　4 (+12%) |
| rROD in ppFEV1 of 80% (base case 90%) | F/F | $| | 5.08 | $　|　4 (+14%) |
| F/MF | $| | 6.95 | $　|　4 (+11%) |
| Combined | $| | 5.80 | $　|　4 (+13%) |
| Same costs of ELX/TEZ/IVA as listed for the ≥12 years | F/F | $| | 5.72 | $|7 (-15%) |
| F/MF | $| | 7.66 | $|7 (-11%) |
| Combined | $| | 6.46 | $|7 (-13%) |

Source: Table 3.1.32, pp175-177 of the submission; developed as part of the Commentary.

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; ppFEV1 = percent predicted forced expiratory volume in one second; QALYs = quality-adjusted life-years; rROD = relative rate of reduction in decline.

Note: a Table 4, ELX/TEZ/IVA PSD, December 2021

*The redacted values correspond to the following ranges:*

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

*2 $55,000 to < $75,000*

*3 $95,000 to < $115,000*

*4 $155,000 to < $255,000*

*5 $355,000 to < $455,000*

*6 $255,000 to < $355,000*

*7 $115,000 to < $135,000*

* 1. The ESC noted the economic model assumed LoE after || || years for ELX/TEZ/IVA and | | years of LUM/IVA after which generic entry would result in a 90% price reduction. The ESC reiterated its previous consideration that modelling decreases due to LoE was not appropriate (paragraph 6.50, ELX/TEZ/IVA PSD, March2021 PBAC meeting). The ESC noted price reductions due to LoE previously claimed have not been realised as new treatments have become available before the price reduction occurs. The ESC noted removal of the LoE assumption increased the ICERs substantially, particularly for the F/MF population (74% increase).
  2. The ESC noted the economic model assumed compliance of 90% which was lower than the trial compliance of 100%. The ESC reiterated this was inappropriate and that the use of compliance lower than in the trials and assuming the same treatment effect as in the trials was not justified by the submission (paragraph 6.47, ELX/TEZ/IVA PSD, March 2021 PBAC meeting).
  3. The ESC considered it remained unclear what the appropriate cost per patient per year is for the additional treatment due to starting treatment at a younger age. The ESC noted in the initial years of treatment the absolute increase in ppFEV1 would likely be smaller in patients aged 6 to 11 years compared with those aged ≥12 years as the lung function in the young patients is, on average, higher. This potentially suggests the cost per patient per year should be lower in the younger patients. Overall, the ESC considered the magnitude of benefit associated with earlier treatment is unknown and hence the appropriate cost per patient for the additional years of treatment is also largely unknown.
  4. For F/RF and F/R117H patients, the submission proposed the listing of ELX/TEZ/IVA at the same price as LUM/IVA and TEZ/IVA stating that the proposed price will be economically attractive given the superior treatment effect associated with ELX/TEZ/IVA over LUM/IVA and TEZ/IVA.For F/G patients, the submission proposed the same effective price of ELX/TEZ/IVA used for F/F and F/MF in the economic model arguing that this will result in cost-savings given the superior efficacy of ELX/TEZ/IVA compared to IVA. Given the high cost of ivacaftor, the claimed cost saving for F/G patients seemed reasonable. However, there are limitations associated with extrapolating the clinical efficacy from evidence in patients ≥12 years.
  5. The calculation of the proposed effective price is presented in Table 17. The proposed effective price for patients aged 6 to 11 years for which evidence is available (F/F and F/MF patients) is higher than the agreed price for patients aged ≥12 years. The requested annual effective price of ELX/TEZ/IVA for the proposed listing was calculated as the weighted price across the subpopulations as $| | ($| | per pack; 13.04 packs per year). This is higher than the current annual effective price for the ≥12 years patients of $| | per patient per year ($| | per pack; 13.04 packs per year).

Table 17: ELX/TEZ/IVA requested effective prices for patients initiating therapy aged 6-11 years

|  |  |  |  |
| --- | --- | --- | --- |
| **Subpopulation** | **Proportion (%)a** | **Effective price per patient per year**  **(assuming 13.04 packs per year i.e., 100% compliance)** | **Basis of price** |
| F/F | 48.93% | $| | CEA vs LUM/IVA |
| F/MF | 30.41% | $| | CEA vs BSC |
| F/G | 7.21% | $| | Same price as F/F and F/MF population |
| F/RF | 7.99% | $|b | Same price as LUM/IVA |
| F/R117H | 5.46% | $|b | Same price as LUM/IVA |
| Total | 100.00% | $| | Weighted price  $　|　 per pack (assuming 95% x 13.04 = 12.39 packs per year) |
| Current effective price for the listing of patients ≥12 years) | | $| | $　|　 per pack (assuming 90% x 13.04 = 11.74 packs per year) |

Source: Table 3.2.2, p180 of the submission.

BSC = best supportive care; CEA = cost effectiveness analysis; CF = Cystic Fibrosis; CM = cost minimisation; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; 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/NYC = F not yet characterised; F/RF = heterozygous for F508del-CFTR with a second residual function mutation; LUM/IVA = lumacaftor/ ivacaftor

Note: Rounding applies.

a ACFDR 2021 requested data by the sponsor  
b Consistent with agreed price of $|| for 11 packs

* 1. The pre-PBAC response proposed an ex-manufacturer price per pack for patients aged 6 to 11 years ($| |) that is equivalent to that agreed for the PBS listing for patients aged ≥12 years. The pre-PBAC response stated that at this pack price, the weighted cost per patient per year is $| | (assuming 100% compliance; noted to be $| | in Table 17 due to rounding of pack sizes).
  2. The pre-PBAC response calculated a cost per patient per year for the F/F and F/MF population of $| | (assuming 100% compliance) based on achieving the weighted price outlined in paragraph 6.59 using the proportion of patients over 6 years of age across the populations. The PBAC noted the methodology for calculating the weighted price was different to the approach in the submission (which used the proportion of patients aged 6 to 11 years), however, acknowledged this was likely to have only resulted in the cost per patient in the F/F and F/MF populations being slightly overestimated. The PBAC noted the base case model provided with the pre-PBAC response, using a cost per patient per year of $| | ($| | x 90% compliance) and 80% rROD (as accepted in the pre-PBAC response, refer paragraph 6.45), resulted in a combined ICER of $135,000 to < $155,000/QALY ($135,000 to < $155,000/QALY in the F/F population and $135,000 to < $155,000/QALY in the F/ MF population).

Drug cost/patient/year

* 1. The price per pack for ELX/TEZ/IVA in the economic model provided with the submission was the specific price for the F/F and F/MF subpopulations ($| |), whereas the price per pack used in the financial estimates was the weighted price across all subpopulations ($| |).
  2. The ELX/TEZ/IVA price per pack for the F/F and F/MF populations in the economic model was revised to $| | and the weighted price used in the financials was revised to $| | per pack in the pre-PBAC response. The drug cost per patient per year in the economic model and the financial estimates using the revised costs are summarised in Table 18. For simplicity, these costs include compliance but exclude discontinuations.

Table 18: Drug cost per patient for proposed and comparator drugs (using revised unit price provided in pre-PBAC response)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **ELX/ TEZ/ IVA** | | **LUM/ IVA (for F/F population only)** | |
| **Economic model**  **(F/F and F/ MF population** | **Financial estimates**  **(F/any population)** | **Economic model** | **Financial estimates** |
| Price per pack/ 28-day supply (A) | $| | | $| | | $| | | $| | |
| Compliance (B) | 90% | 95% | 90% | 84.4%1 |
| Cost/ patient/ year ((365.25/28) pack/year\* A\*B) | $| | | $| | | $| | | $| | |

1. Calculated as 11/13.04

Estimated PBS usage & financial implications

* 1. This submission was not considered by DUSC.
  2. The submission used two approaches to estimate the number of eligible patients: (1) the number of patients who are currently eligible for PBS listed CFTR modulators were estimated from the subsidisation caps in existing Deeds and (2) the number of patients who are not currently eligible for PBS listed CFTRs were estimated from epidemiological data (Table 19).

Table 19**: Epidemiological data used to estimate the number of patients eligible for ELZ/TEZ/IVA**

|  |  |  |  |
| --- | --- | --- | --- |
| **Population**  **(6 to 11 years)** | **Number of patients in ACFDR analysis (actual 2020)** | **Number of patients in ACFDR analysis (estimated 2023, assumed to be Year 1)** | **% of overall F/ any aged 6 to 11 years of age** |
| F/F | 251 | 263 | 48.93% |
| F/RF | 41 | 43 | 7.99% |
| F/G | 37 | 39 | 7.21% |
| F/MF | 156 | 164 | 30.41% |
| F/R117H | 28 | 29 | 5.46% |
| Total | 513 | 538 | 100% |

Source: TRI6-11\_UCM-Release-3-Workbook-v018.xls

ACFDR = Australian Cystic Fibrosis Disease Registry; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; F/G = CF patient heterozygous for the F508del in the CFTR gene with a gating mutation; F/F = homozygous for F508del-CFTR mutations; F/MF = heterozygous for F508del-CFTR mutation with a second minimal function allele; F/R117H = CF patients who are heterozygous for F508del in the CFTR gene with a R117H mutation; F/RF = heterozygous for F508del-CFTR with a second residual function mutation.

* 1. A summary of the estimated number of treated patients is presented in Table 20. The submission stated the approach to estimating utilisation was consistent with the approach used for the ≥12 years population.

Table 20: Estimation of number of treated patients

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** | **Year 6** |
| **Patients included within the subsidisation caps under existing Deeds (calculated from subsidisation caps in existing Deed)** | | | | | | |
| Estimated number of F/F patients on LUM/IVAa | ||1 | ||1 | |　1 | ||1 | |　1 | |||1 |
| F/F patients on LUM/IVA switching to ELX/TEZ/IVA (100% switch) | ||1 | ||1 | |　1 | ||1 | |　1 | |||1 |
| Estimated number of F/G patients on IVAb | ||1 | ||1 | |　1 | ||1 | |　1 | |||1 |
| F/G patients on IVA switching to ELX/TEZ/IVA (100% switch) | ||1 | ||1 | |　1 | ||1 | |　1 | |||1 |
| Total treated population | ||1 | ||1 | |　1 | ||1 | |　1 | |||1 |
| **Patients not currently eligible for PBS-reimbursed CFTR modulators (using epidemiological approach)** | | | | | | |
| F/MF prevalent population | ||1 | ||1 | |　1 | ||1 | |　1 | ||1 |
| Treated F/MF patients (98% uptake and applying discontinuation ratesc) | ||1 | ||1 | |　1 | ||1 | |　1 | |||1 |
| F/RF population | ||1 | ||1 | |　1 | ||1 | |　1 | ||1 |
| Treated F/RF patients (80% uptake and applying discontinuation ratesc) | ||1 | ||1 | |　1 | ||1 | |　1 | ||1 |
| F/F117H population | ||1 | ||1 | |　1 | ||1 | |　1 | ||1 |
| Treated F/R117H patients (80% uptake and applying discontinuation ratesc) | ||1 | ||1 | |　1 | ||1 | |　1 | ||1 |
| Total treated population | ||1 | ||1 | |　1 | ||1 | |　1 | ||1 |
| **F/F patients not captured in the Deed calculations** | | | | | | |
| Total F/F not captured in the Deeds | ||1 | ||1 | |　1 | ||1 | |　1 | ||1 |
| Treated F/F not captured in the Deeds (98% uptake and applying discontinuation ratesc) | ||1 | ||1 | |　1 | ||1 | |　1 | ||1 |
| Total all subpopulations treated with ELX/TEZ/IVA | ||2 | ||2 | |　2 | ||2 | |　2 | ||2 |

Source: TRI6-11\_UCM-Release-3-Workbook-v018.xls, Worksheet 10.Registry population,

CFTR = Cystic fibrosis transmembrane conductance regulator; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; F/G = CF patient heterozygous for the F508del in the CFTR gene with a gating mutation; F/F = homozygous for F508del-CFTR mutations; F/MF = heterozygous for F508del-CFTR mutation with a second minimal function allele; F/R117H = CF patients who are heterozygous for F508del in the CFTR gene with a R117H mutation; F/RF = heterozygous for F508del-CFTR with a second residual function mutation; LUM/IVA = lumacaftor; PBS = Pharmaceutical Benefits Scheme;

a (annual agreed caps for LUM/IVA for F/F patients aged ≥ 2 years and TEZ/IVA for F/F and RF heterozygous patients aged ≥ 12 years) x (92%; estimated F/F patients aged ≥ 2 years) x (16%; F/F patients aged 6 to 11)/($| |; agreed cost per patient per year).

b (annual agreed previous IVA subsidisation caps for CF patients who have a G551D mutation or other gating (class III) mutation on at least one allele and who are aged ≥ 12 months) x (15%; A gating mutation on ≥ 1 allele patients aged 6–11 yrs) x (86%; F508del mutation (F/G) aged 6–11 yrs)/($| |; agreed cost per patient per year)

c1.4% in Yr 1, 4.2% in Yr 2

*The redacted values correspond to the following ranges:*

*1 < 500*

*2 500 to < 5000*

* 1. The submission stated that the number of eligible patients estimated using the caps for the F/F population (i.e., < 500 in Year 1) was lower than the number of patients reported in the ACFDR (263), hence it was deemed appropriate to estimate how many patients were not being captured within the existing caps. Of the additional < 500 patients, < 500 are currently accessing ELX/TEZ/IVA in clinical trials or through compassionate access.
  2. The submission stated the discontinuation rates for ELX/TEZ/IVA were derived from long-term clinical trials for patients aged over 12 years of age and are expected to be reflective of patients in the requested population (1.4% in Year 1, 4.2% in Year 2). This is lower than the discontinuation rates accepted for the over 12 population (2.6% in Year 1, 7.3% in Year 2) (paragraph 5.17, ELX/TEZ/IVA PSD, December 2021 PBAC meeting). The PSCR stated the discontinuation rates applied to the 6 to 11 year population are based on clinical evidence and real-world experience and contends it is not appropriate to apply the rates used for the ≥12 population*.*
  3. The proportion of patients switching and uptake rates are summarised in Table 21. The submission did not assume gradual switch or uptake with all patients initiating treatment with ELX/TEZ/IVA in the first year.

Table 21: Proportion of patients switching CFTR treatments and uptake rates

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Accepted for over 12 years** | **Proposed for 6 to 11 years** | **Comment** |
| F/F population | | | |
| switch (in patients covered by Deed) | 90% | 100% | Over 12 years switching from TEZ/IVA, 6 to 11 years switching from LUM/IVA.  May be overestimated. |
| uptake (in patients not covered by Deed) | 70% in Yr 1 to 75% in Yr 6 | 98% | May be overestimated |
| F/G | | | |
| switch (in patients covered by Deed) | 60% in Yr 1, 80% Yr 2 to 6 | 100% | May be overestimated |
| uptake (in patients not covered by Deed) | 40% in Yr 1 to 60% in Yr 6 | - |  |
| F/MF | | | |
| uptake | 95% | 98% | Uncertain if higher uptake reasonable. |
| F/RF | | | |
| Switch (in patients covered by Deed) | 90% | - | No current treatment option for population aged 6 to 11 years. |
| uptake | 40% in Year 1 to 60% in Year 6 | 80% |  |
| F/R117H | | | |
| uptake | 60% | 80% | Uncertain if higher uptake reasonable. |

CFTR = Cystic fibrosis transmembrane conductance regulator; F/G = CF patient heterozygous for the F508del in the CFTR gene with a gating mutation; F/F = homozygous for F508del-CFTR mutations; F/MF = heterozygous for F508del-CFTR mutation with a second minimal function allele; F/R117H = CF patients who are heterozygous for F508del in the CFTR gene with a R117H mutation; F/RF = heterozygous for F508del-CFTR with a second residual function mutation; LUM/IVA = lumacaftor ivacaftor; TEZ/ IVA = tezacaftor ivacaftor

* 1. The PSCR stated uptake in younger age groups is expected to be higher and faster (than in the older patients), primarily due to parental management of treatment, whereby the vast majority will elect for treatment that prevents disease progression and lung damage in their child as soon as they are eligible. In addition to a high uptake in Year 1, the ESC noted it was assumed all patients would receive a full year of treatment which would require everyone to initiate treatment on the first day of listing.
  2. The submission assumed compliance to be 95%, informed by internal Australian market data of patients aged 6–11 years on existing CFTR modulators, and of ELX/TEZ/IVA compliance in global markets. The submission further stated that it has been consistently observed that compliance is higher in younger populations due to parental supervision. The use of a compliance rate of 95% is inconsistent with the 90% used in the economic model and higher than the 90% accepted for the ≥12 years population (paragraph 8.1, ELX/TEZ/IVA PSD, December 2021).
  3. A summary of the estimated use and financial implications is presented in Table 22.

Table 22: **Estimated use and financial implications (using pack price as revised in pre-PBAC response)**

|  | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
| --- | --- | --- | --- | --- | --- | --- |
| Estimated extent of use | | | | | | |
| Total number of F/any patients treated | 517 | 517 | 519 | 528 | 537 | 545 |
| Number of scripts dispenseda | 6,403 | 6,408 | 6,437 | 6,544 | 6,651 | 6,760 |
| Estimated financial implications of ELX/TEZ/IVA | | | | | | |
| Cost to PBS/RPBS less co-payments | $|1 | $　|　1 | $　|　1 | $　|　5 | $　|　5 | $　|　5 |
| **Estimated financial implications for LUM/IVA and IVA monotherapy** | | | | | | |
| Cost to PBS/RPBS less co-payments | |2 | |2 | |2 | |2 | |2 | |2 |
| Net financial implications | | | | | | |
| Net cost to PBS/RPBS | $|3 | $　|　3 | $　|　3 | $　|　3 | $　|　3 | $　|　3 |
| Net cost to MBS | $|4 | $　|　4 | $　|　4 | $　|　4 | $　|　4 | $　|　4 |
| Net cost to PBS/RPBS/MBS | $　|　3 | $　|　3 | $　|　3 | $　|　3 | $　|　3 | $　|　3 |

Source: Table 4.3.9, p198; Table 4.3.3, p199; Table 4.7.2, p211, Table 4.9.1, p213 of the submission.

ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; IVA = ivacaftor; LUM/IVA = lumacaftor/ivacaftor; MBS= Medicare Benefit Schedule; PBS=Pharmaceutical Benefit Scheme; RPBS = Repatriation Schedule of Pharmaceutical Benefits

Note

a Assuming 12.84 scripts per year as estimated by the submission.

*The redacted values correspond to the following ranges:*

*1 $50 million to < $60 million*

*2 Net cost saving*

*3 $30 million to < $40 million*

*4 $0 to < $10 million*

*5 $60 million to < $70 million*

* 1. The total net cost to the PBS/RPBS of listing ELX/TEZ/IVA was estimated to be $30 million to < $40 million in Year 6, and a total of $200 million to < $300 million in the first 6 years of listing. The total cost to the PBS/RPBS was likely overestimated due to the likely overestimated number of patients and the overly high compliance rates used.
  2. The ESC considered that, overall, the approach to the financial estimates was reasonable but the number of patients likely to be treated was overestimated, particularly in the first year of listing.

Financial Management – Risk Sharing Arrangements

* 1. No risk sharing arrangement was proposed in the submission.

1. PBAC Outcome
   1. The PBAC recommended elexacaftor/ tezacaftor/ ivacaftor (ELZ/TEZ/IVA) for the treatment of cystic fibrosis in patients who are aged 6 to 11 years and who have at least one F508del mutation on the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The PBAC noted the evidence presented could not accurately quantify the benefit of treating patients with ELX/TEZ/IVA from a younger age but acknowledged treatment from a young age was likely to be beneficial. The PBAC considered ELX/TEZ/IVA was likely to be cost-effective for this population at a unit price no higher than that of the current PBS listing (for patients over 12 years of age) as proposed by the sponsor in its pre-PBAC response. The PBAC considered a number of assumptions applied in the financial estimates were overly optimistic and should be reduced to be consistent with the assumptions applied to the financial estimates agreed for the population of patients over 12 years of age.
   2. The PBAC noted the strong consumer support for extending the availability of ELX/TEZ/IVA to CF patients aged 6 to 11 years.
   3. The PBAC noted the submission nominated LUM/IVA as comparator in the F/F population, IVA monotherapy as comparator in the F/G population and BSC as comparator in the F/MF, F/RF and F/R117H populations. The PBAC considered the nominated comparators were reasonable; however, it would have been informative to compare commencing treatment with ELX/TEZ/IVA between the ages of 6-11 years with commencing treatment with ELX/TEZ/IVA at 12 years of age or older in each of these populations.
   4. The PBAC was satisfied that ELX/TEZ/IVA provides, for some patients, an improvement in efficacy over the nominated comparators.
   5. The PBAC advised the following with regards to the restriction criteria:

* The population criteria in the current listing for ELX/TEZ/IVA “Patient must be 12 years of age or older” should be amended to “Patient must be at least 6 years of age”;
* An item be added for the new presentation (elexacaftor 50 mg/ tezacaftor 25 mg/ ivacaftor 37.5 mg film-coated tablets co-packaged with ivacaftor 75 mg film-coated tablets) with the same restriction criteria as the current listing except for the population criteria “Patient must be aged between 6 and 11 years inclusive”.
  1. The PBAC noted the submission presented one randomised controlled trial of ELX/TEZ/IVA versus placebo (representing best supportive care) in the F/MF population (Study 116, n=121). The PBAC noted that treatment with ELX/TEZ/IVA provided a significant improvement in outcomes of ppFEV1, CFQ-R Respiratory Domain, sweat chloride and lung clearance index (LCI). The PBAC noted the improvement in ppFEV1 (which the PBAC considered was the outcome most likely to be related to long term benefit) was greater than the MCID of 10% at 24 weeks (11.0%).
  2. The PBAC noted the submission presented an unanchored indirect treatment comparison of ELX/TEZ/IVA and LUM/IVA in the F/F population (ELX/TEZ/IVA, Study 106, n=29 and LUM/IVA, pooled results from Study 109/ Study 011, n=160). The PBAC noted the improvement in ppFEV1 was greater than the MCID at 24 weeks (11.5%). The PBAC noted the benefit of ELX/TEZ/IVA was supported by data to 120 weeks from Study 107, an extension to Study 106 (which also included the F/MF population).
  3. The PBAC noted the submission did not present evidence for the F/RF, F/G or F/R117H populations aged 6 to 11 years but considered the results in studies in patients ≥12 years of age supported the likely benefit of ELX/TEZ/IVA in the younger age group.
  4. The PBAC considered the magnitude of benefit of commencing ELX/TEX/IVA before 12 years of age was not able to be quantified with the available data; however, acknowledged that preventing decline in lung function from a younger age was likely to be beneficial.
  5. The PBAC considered the claim that ELX/TEZ/IVA is of comparable safety to the nominated comparators in the 6 to 11 years population was reasonable.
  6. The PBAC noted that, with the price and model parameters proposed in the pre-PBAC response (see paragraph 6.61), the incremental cost effectiveness ratio (ICER) for the F/F population was $135,000 to < $155,000 per QALY gained and for the F/MF population was $135,000 to < $155,000 per QALY gained. The PBAC noted the economic model resulted in a substantial increase in median life expectancy for patients starting ELX/TEZ/IVA between 6 and 11 years of age compared to commencing ≥12 years of age which was not supported by the clinical data presented. As a result, the PBAC considered the ICERs to be uncertain, however based on the available evidence, the PBAC considered it plausible that ELZ/TEZ/IVA would be cost-effective in this population at a unit price no higher than that for the ≥12 years population.
  7. The PBAC considered the methodology for estimating the number of patients likely to be treated with ELX/TEZ/IVA was reasonable; however, the patient numbers were overestimated due to a number of optimistic assumptions which were not well supported. The PBAC advised a number of assumptions, including the discontinuation rates (paragraph 6.67) and uptake/switch rates (Table 21), should be amended to be consistent with what was accepted for the ≥12 year population. The PBAC further advised it would be appropriate to assume 90% compliance consistent with that used in the economic model.
  8. The PBAC advised that the extended population should be included in the existing Risk Sharing Arrangement for ELX/TEZ/IVA, LUM/IVA and TEZ/IVA. Based on the revised financial estimates outlined in paragraph 7.12, the PBAC advised the net cost of listing ELX/TEZ/IVA for patients aged 6 to 11 years could be added to the expenditure caps currently in place. The PBAC considered the net cost of listing ELX/TEZ/IVA should take into account the reduced utilisation of LUM/IVA and IVA, and that the separate expenditure caps currently in place for IVA should be adjusted accordingly.
  9. 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:

1. Based on the available evidence the magnitude of benefit of starting treatment from a younger age was not able to be quantified and therefore the criteria of having a substantial and clinically relevant improvement in efficacy compared to starting at an older age was not met;
2. The treatment is expected to address a high and urgent unmet clinical need for the F/MF, F/RF and R/R117H populations as they currently have no alternative treatment options (until they are at least 12 years of age);
3. 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.
   1. The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

1. Recommended listing
   1. Amend existing listing:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT**  **medicinal product pack** | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№.of**  **Rpts** | **Available brands** |
| ELEXACAFTOR+TEZACAFTOR+IVACAFTOR (&) IVACAFTOR | | | | | |
| elexacaftor 100 mg + tezacaftor 50 mg + ivacaftor 75 mg tablet [56] (&) ivacaftor 150 mg tablet [28], 84 | 12936W (public)  12938Y private) | 1  1 | 1  1 | 5  5 | Trikafta |
|  | | | | | |
| **Restriction Summary [new] / Treatment of Concept: [new]** | | | | | |
| **Category / Program:** Section 100 – Highly Specialised Drugs Program | | | | | |
| **Prescriber type:** Medical Practitioners | | | | | |
| **Restriction type:**  Authority Required (in writing only via post/HPOS upload) | | | | | |
|  | | | | | |

|  |  |
| --- | --- |
| **Edit Restriction Summary 12961 / ToC: 12972: Authority Required** | |
| **Concept ID**  (for internal Dept. use) |  |
|  |
|  |
|  | **Condition:** Cystic fibrosis |
|  | **Indication:** Cystic fibrosis |
|  |  |
|  | **Treatment Phase:** Initial treatment |
|  |  |
|  | **PR level administrative advice** |
|  | **Administration advice:**  No increase in the maximum quantity or number of units may be authorised. |
|  | **Administration advice:**  No increase in the maximum number of repeats may be authorised |
|  | **Administration advice:**  Special Pricing Arrangements apply. |
|  | **Administrative Advice:**  For the purposes of this restriction, PBS-subsidised 'CFTR modulator' means ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor and elexacaftor/ tezacaftor/ ivacaftor. |
|  | **Administrative Advice:**  Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).  Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au  Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos  Or mailed to:  Services Australia  Complex Drugs  Reply Paid 9826  HOBART TAS 7001 |
|  |  |
|  | **Treatment criteria:** |
|  | Must be treated by a specialist respiratory physician with expertise in cystic fibrosis or in consultation with a specialist respiratory physician with expertise in cystic fibrosis if attendance is not possible due to geographic isolation |
|  | **AND** |
|  | **Treatment criteria:** |
|  | Must be treated in a centre with expertise in cystic fibrosis or in consultation with a centre with expertise in cystic fibrosis if attendance is not possible due to geographic isolation |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must have at least one F508del mutation in the cystic fibrosis transmembrane conductance (CFTR) gene |
|  | **AND** |
|  | **Clinical criteria:** |
|  | The treatment must be given concomitantly with standard therapy for this condition |
|  | **AND** |
|  | **Clinical Criteria:** |
|  | Patient must have either chronic sinopulmonary disease or gastrointestinal and nutritional abnormalities, prior to initiating treatment with this drug |
|  | **Population criteria:** |
|  | Patient must be ~~12 years of age or older~~ *at least 6 years of age* |
|  |  |
|  | **Prescribing instructions:**  This pharmaceutical benefit is not PBS-subsidised for this condition in a patient who is currently receiving one of the strong CYP3A4 inducers outlined in the Product Information. |
|  | **Prescribing instructions:**  The authority application must be in writing and must include:  (1) a completed authority prescription; and  (2) a completed Cystic Fibrosis Authority Application Supporting Information Form; and  (3) details of the pathology report substantiating the patient having at least one F508del mutation - quote each of the: (i) name of the pathology report provider, (ii) date of pathology report, (iii) unique identifying number/code that links the pathology result to the individual patient; and  (4) current CYP3A4 inhibitors, CYP3A4 inducers and IV antibiotics |
|  | |
| **Edit Restriction Summary 12942 / ToC: 12962: Authority Required** | |
|  |  |
|  | **Treatment Phase:** Continuing treatment |
|  |  |
|  | **Treatment criteria:** |
|  | Must be treated by a specialist respiratory physician with expertise in cystic fibrosis or in consultation with a specialist respiratory physician with expertise in cystic fibrosis if attendance is not possible due to geographic isolation |
|  | **AND** |
|  | **Treatment criteria:** |
|  | Must be treated in a centre with expertise in cystic fibrosis or in consultation with a centre with expertise in cystic fibrosis if attendance is not possible due to geographic isolation |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must have previously received PBS-subsidised treatment with this drug for this condition |
|  | **AND** |
|  | **Clinical criteria:** |
|  | The treatment must be given concomitantly with standard therapy for this condition. |
|  | **AND** |
|  | **Population criteria:** |
|  | Patient must be ~~12 years of age or older~~ *at least 6 years of age* |
|  |  |
|  | **Prescribing instructions:**  This pharmaceutical benefit is not PBS-subsidised for this condition in a patient who is currently receiving one of the strong CYP3A4 inducers outlined in the Product Information. |
|  | The authority application must be in writing and must include:  (1) a completed authority prescription form; and  (2) a completed Cystic Fibrosis elexacaftor, tezacaftor with ivacaftor Authority Application Supporting Information Form; and  (3) current CYP3A4 inhibitors, CYP3A4 inducers and IV antibiotics. |

* 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 50 mg + tezacaftor 25 mg + ivacaftor 37.5 mg [56] (&) ivacaftor 75 mg [28], 84 | NEW (public)  NEW private) | 1  1 | 1  1 | 5  5 | Trikafta |
|  | | | | | |
| **Restriction Summary [new] / Treatment of Concept: [new]** | | | | | |
| **Category / Program:** Section 100 – Highly Specialised Drugs Program | | | | | |
| **Prescriber type:** Medical Practitioners | | | | | |
| **Restriction type:**  Authority Required (in writing only via post/HPOS upload) | | | | | |
|  | | | | | |

|  |  |
| --- | --- |
| **Restriction Summary [new] / ToC: [new]: Authority Required** | |
| **Concept ID**  (for internal Dept. use) | **Category / Program:** Section 100 – Highly Specialised Drugs Program [Public and Private Hospitals] |
| **Prescriber type:** Medical Practitioners |
| **Restriction type:** Authority Required – non-immediate/delayed assessment by Services Australia |
|  | **Condition:** Cystic fibrosis |
|  | **Indication:** Cystic fibrosis |
|  |  |
|  | **Treatment Phase:** Initial treatment |
|  |  |
|  | **PR level administrative advice** |
|  | **Administration advice:**  No increase in the maximum quantity or number of units may be authorised. |
|  | **Administration advice:**  No increase in the maximum number of repeats may be authorised |
|  | **Administration advice:**  Special Pricing Arrangements apply. |
|  | **Administrative Advice:**  For the purposes of this restriction, PBS-subsidised 'CFTR modulator' means ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor and elexacaftor/ tezacaftor/ ivacaftor. |
|  | **Administrative Advice:**  Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).  Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au  Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos  Or mailed to:  Services Australia  Complex Drugs  Reply Paid 9826  HOBART TAS 7001 |
|  |  |
|  | **Treatment criteria:** |
|  | Must be treated by a specialist respiratory physician with expertise in cystic fibrosis or in consultation with a specialist respiratory physician with expertise in cystic fibrosis if attendance is not possible due to geographic isolation |
|  | **AND** |
|  | **Treatment criteria:** |
|  | Must be treated in a centre with expertise in cystic fibrosis or in consultation with a centre with expertise in cystic fibrosis if attendance is not possible due to geographic isolation |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must have at least one F508del mutation in the cystic fibrosis transmembrane conductance (CFTR) gene |
|  | **AND** |
|  | **Clinical criteria:** |
|  | The treatment must be given concomitantly with standard therapy for this condition. |
|  | **AND** |
|  | **Clinical Criteria:** |
|  | Patient must have either chronic sinopulmonary disease or gastrointestinal and nutritional abnormalities, prior to initiating treatment with this drug |
|  | **Population criteria:** |
|  | Patient must be aged between 6 and 11 years inclusive. |
|  |  |
|  | **Prescribing instructions:**  This pharmaceutical benefit is not PBS-subsidised for this condition in a patient who is currently receiving one of the strong CYP3A4 inducers outlined in the Product Information. |
|  | **Prescribing instructions:**  The authority application must be in writing and must include:  (1) a completed authority prescription; and  (2) a completed Cystic Fibrosis Authority Application Supporting Information Form; and  (3) details of the pathology report substantiating the patient having at least one F508del mutation - quote each of the: (i) name of the pathology report provider, (ii) date of pathology report, (iii) unique identifying number/code that links the pathology result to the individual patient; and  (4) current CYP3A4 inhibitors, CYP3A4 inducers and IV antibiotics |
|  | |
| **Restriction Summary [new] / ToC: [new]: Authority Required** | |
|  |  |
|  | **Treatment Phase:** Continuing treatment |
|  |  |
|  | **Treatment criteria:** |
|  | Must be treated by a specialist respiratory physician with expertise in cystic fibrosis or in consultation with a specialist respiratory physician with expertise in cystic fibrosis if attendance is not possible due to geographic isolation |
|  | **AND** |
|  | **Treatment criteria:** |
|  | Must be treated in a centre with expertise in cystic fibrosis or in consultation with a centre with expertise in cystic fibrosis if attendance is not possible due to geographic isolation |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must have previously received PBS-subsidised treatment with this drug for this condition |
|  | **AND** |
|  | **Clinical criteria:** |
|  | The treatment must be given concomitantly with standard therapy for this condition. |
|  | **AND** |
|  | **Population criteria:** |
|  | Patient must be aged between 6 and 11 years inclusive. |
|  |  |
|  | **Prescribing instructions:**  This pharmaceutical benefit is not PBS-subsidised for this condition in a patient who is currently receiving one of the strong CYP3A4 inducers outlined in the Product Information. |
|  | The authority application must be in writing and must include:  (1) a completed authority prescription form; and  (2) a completed Cystic Fibrosis elexacaftor, tezacaftor with ivacaftor Authority Application Supporting Information Form; and  (3) current CYP3A4 inhibitors, CYP3A4 inducers and IV antibiotics. |

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

1. 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.

1. Sponsor’s Comment

The sponsor had no comment.

Addendum to the November 2022 PBAC PSD:

**4.04 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   
Trikafta®  
VERTEX PHARMACEUTICALS (AUSTRALIA) PTY. LTD.**

1. Background
   1. In November 2022, the PBAC recommended elexacaftor/tezacaftor/ivacaftor (ELZ/TEZ/IVA) for the treatment of cystic fibrosis in patients who are aged 6 to 11 years and who have at least one F508del mutation on the cystic fibrosis transmembrane conductance regulator (CFTR) gene.
   2. The PBAC considered a number of assumptions applied in the financial estimates were overly optimistic and should be reduced to be consistent with the assumptions applied to the financial estimates agreed for the population of patients over 12 years of age (YOA) (see paragraph 7.12).
   3. As part of the post-PBAC process, the sponsor provided a pricing proposal that was not consistent with the Public Summary Document (PSD) as it did not change the assumptions applied to the financial estimates as advised.
   4. As the listing was unable to be progressed with financial estimates that were not consistent with the PSD, the sponsor requested consideration by the PBAC. The sponsor stated it did not consider the assumptions applied were overly optimistic and provided additional information to support the assumptions applied in the financial estimates.
2. PBAC Outcome
   1. The PBAC revised its previous advice regarding the recommendation of elexacaftor/ tezacaftor/ ivacaftor (ELZ/TEZ/IVA) for the treatment of cystic fibrosis in patients who are aged 6 to 11 years and who have at least one F508del mutation on the cystic fibrosis transmembrane conductance regulator (CFTR) gene.
   2. The PBAC noted the financial estimates proposed by the sponsor assumed an overall uptake of 96% in eligible patients in Year 1, compared to approximately 80% in Year 1 if the uptake rates advised by the PBAC in November 2022 were applied.
   3. The PBAC noted the experience in overseas’ markets where ELX/TEZ/IVA is reimbursed in patients aged 6 to 11 years and the high and rapid uptake in the 12 years and older population in Australia since PBS listing in April 2022. The PBAC considered that the experience of CF clinics gained in treating the population of patients 12 years and older would facilitate rapid initiation of patients aged 6 to 11 years.
   4. The PBAC noted some additional clinical data in patients aged 6 to 11 years was provided to support the use of the discontinuation rates applied in the financial estimates (1.4% in Year 1, 4.2% in Year 2).
   5. The PBAC noted the sponsor stated the full year net Commonwealth expenditure for the current combined Deed (covering LUM/IVA, TEZ/IVA and ELX/TEZ/IVA) is expected to exceed the cap by | |%. The PBAC recalled when it previously reviewed this data, expenditure was at | |% of caps with 6 months of data available.
   6. The PBAC considered that, overall, based on the additional information provided by the sponsor, it was reasonable for the assumptions informing the financial estimates for the population aged 6 to 11 years to be different to those informing the population aged 12 years and over as it was likely uptake would be higher and more rapid than initially predicted for the older age group.
   7. The PBAC noted the financial estimates provided in the pricing proposal were consistent with the estimates presented in the November 2022 submission (Table 22), with the small difference being due to the reduction in copayments. The PBAC noted that, overall, the additional cost of listing ELX/TEZ/IVA in patients who are aged 6 to 11 years as proposed by the sponsor, compared to the revised financial estimates based on assumptions as advised by the PBAC in November 2022 was approximately $50 million to < $60 million over 6 years.
   8. The PBAC reiterated the advice that the extended population should be included in the existing Risk Sharing Arrangement for ELX/TEZ/IVA, LUM/IVA and TEZ/IVA and that the net cost of listing ELX/TEZ/IVA should take into account the reduced utilisation of LUM/IVA and IVA. The PBAC further noted that this approach will also result in an adjustment of the separate expenditure caps currently in place for IVA.

**Outcome**:

Recommend

1. 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.

1. Sponsor’s Comment

Vertex welcomes the positive recommendation from PBAC for these young patients, particularly the recommendation that every eligible patient in Australia with at least one *F508del* mutation should have access to TRIKAFTA.

1. Study 116 was not provided with the TGA application [↑](#footnote-ref-2)
2. Results for Study 109 from Table 5, ELX/TEZ/IVA PSD, July 2021 PBAC meeting. [↑](#footnote-ref-3)
3. Results for Study 102 from Table 5, ELX/TEZ/IVA PSD, July 2021 PBAC meeting. [↑](#footnote-ref-4)