

An addendum to these minutes has been included at the end of the document.

5.07 ELEXACAFITOR/TEZACAFITOR/IVACAFITOR

Ellexacafter 100 mg/tezacafter 50 mg/ivacafter 75 mg film-coated tablets co-packaged with ivacafter 150 mg film-coated tablets, TRIKAFTA™, Vertex Pharmaceuticals (Australia) Pty Ltd.

1 Purpose of submission

- 1.1 The submission requested a Section 100, Authority Required listing for ellexacafter/tezacafter/ivacafter (ELX/TEZ/IVA) for the treatment of cystic fibrosis (CF) patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (F/any).
- 1.2 The submission identified five populations who would be eligible for treatment with ELX/TEZ/IVA: (1) patients who are homozygous for the F508del-CFTR mutation (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) and (5) patients who are heterozygous for F508del in the CFTR gene with a second mutation that is unknown or not yet characterised as gating, residual function or minimal function (F/not yet characterised). Clinical evidence and economic analyses were presented for each of these populations (with the exception of the F/ not yet characterised population). The submission stated the efficacy, safety and cost-effectiveness of ELX/TEZ/IVA in the F/MF population is considered to be representative of the F/not yet characterised population.
- 1.3 Listing was requested on the basis of: (1) a cost-effectiveness analysis versus tezacafter/ivacafter (TEZ/IVA) in the F/F population; (2) a cost-effectiveness analysis versus TEZ/IVA in the F/RF population; (3) a cost-analysis versus ivacafter (IVA) in the F/G population; and (4) a cost-effectiveness analysis versus best supportive care (BSC) in the F/MF population.
- 1.4 The key components of the submission are presented in Table 1.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	CF patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (F/any)
Intervention	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	1. TEZ/IVA (Symdeko®) for CF patients aged 12 years and older who are homozygous for the F508del-CFTR mutation (F/F). 2. TEZ/IVA (Symdeko®) for CF patients aged 12 years and older who are heterozygous for F508del in the CFTR gene with a residual function mutation (F/RF). 3. IVA (Kalydeco®) for CF patients aged 12 years and older who are heterozygous for F508del in the CFTR gene with a gating mutation (F/G). 4. BSC for CF patients aged 12 years and older who are heterozygous for F508del in the CFTR gene with a minimal function mutation (F/MF) and for CF patients aged 12 years and older who are heterozygous for F508del in the CFTR gene with a second allele that is unknown and/ or has not yet been characterised as gating, residual function or minimal function (F/not yet characterised)
Outcomes	• Absolute change from baseline in percent predicted forced expiratory volume in one second (ppFEV₁) • Pulmonary exacerbation measures (F/MF population) • Absolute change from baseline in body mass index (F/F, F/MF population) • Absolute change from baseline in CFQ-R Respiratory Domain Score • Absolute change in sweat chloride
Clinical Claim	For CF patients aged 12 years and older 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 to: 1. TEZ/IVA in the F/F population; 2. TEZ/IVA in the F/RF population; 3. IVA in the F/G population; 4. BSC in the F/MF population and the F/not yet characterised population

Source: based on Table 1.1.1 of the submission

Abbreviations: BSC = best supportive care; CF = cystic fibrosis; CFQ-R = Cystic Fibrosis Questionnaire-Revised; 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; IVA = ivacaftor; mg = milligram; ppFEV₁ = percent predicted forced expiratory volume in one second; TEZ/IVA = tezacaftor and ivacaftor

2 Background

Registration status

- 2.1 TGA status at time of PBAC consideration: not registered.
- 2.2 The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration, the Clinical Evaluation Report (CER; round 2), the Delegate's Overview and Advisory Committee on Medicines (ACM) minutes were available.
- 2.3 The ACM considered ELX/TEZ/IVA to have an overall positive benefit-risk profile for the "treatment of cystic fibrosis in patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulatory gene".

Previous PBAC consideration

2.4 The PBAC has previously considered a number of submissions for other CFTR directed therapies for CF; a frame of reference comparison is presented in Table 2.

Table 2: Frame of Reference Comparison

	ELX/TEZ/IVA	TEZ/IVA	LUM/IVA	IVA
Current PBS restriction	F/any: 12 years and older (proposed)	F/F: 12 years and older F/RF: 12 years and older At least one RF: 12 years and older	F/F: 2 years and older	At least one G551D mutation: 12 months of age or older At least one Class III mutation: 12 months of age or older
Current TGA indication	12 and older, have at least one F508del mutation in the CFTR gene (proposed).	12 and older who are homozygous for the F508del mutation or who have at least one mutation in the CFTR gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence	2 and older who are homozygous for F508del in the CFTR gene.	12 months and older who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R 6 years and older who have an R117H mutation in the CFTR gene.
Evidence presented to PBAC	- F/F: Study 103 and Study 109 - F/RF: Study 104 (subgroup) - F/G: Study 104 (subgroup) - F/MF: Study 102 Study 105 (F/F and F/MF, extension study) Up to 48 weeks of data from extension study.	- F/F: EVOLVE, Study 110 (extension study) - F/RF: EXPAND Up to 48 weeks of data from extension study.	2-5 years: Study 115 (non-comparative) 6-11 years: Study 109 and Study 011 (open-label) 12 and older: TRAFFIC, TRANSPORT, PROGRESS (extension) Up to 96 weeks of data from extension studies.	- G551D: STRIVE, ENVISION - Other Class III: KONNECTION Up to 48 weeks of data from extension study.
Comparators	- F/F: TEZ/IVA - F/RF: TEZ/IVA - F/G: IVA - F/MF: BSC	- F/F: LUM/IVA for - F/RF: BSC	BSC	BSC
ppFEV₁ improvement (%)	- F/F: 10.2% vs TEZ/IVA - F/RF: 2.0% vs TEZ/IVA - F/G: 5.8% vs IVA - F/MF: 14.3% vs BSC	- F/F: 1.59% vs LUM/IVA - F/RF: 6.8% vs BSC	2-5 years: 0.5% change from baseline 6-11 years: 3% vs placebo 12 - older: 2.81% vs placebo	10.5% vs placebo
Proposed/current price	\$ [redacted] per 28-day pack (revised to \$ [redacted] in the pre-PBAC response)	Annual price of \$ [redacted] per patient (11 packs per year). Implemented via RSA.	Annual price of \$ [redacted] per patient (11 packs per year). Implemented via RSA.	\$ [redacted] per 28-day pack
Economic evidence	F/F: CUA, ICER \$ [redacted]¹ vs TEZ/IVA	F/F: TEZ/IVA cost-minimised to LUM/IVA (\$ [redacted] per patient)	- CUA 2 years and older: \$ [redacted]² /QALY	G551D: The PBAC considered that the cost-effectiveness of ivacaftor

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ELX/TEZ/IVA	TEZ/IVA	LUM/IVA	IVA
- F/RF: CUA, ICER \$[REDACTED]² vs TEZ/IVA - F/G: Cost-analysis, cost saving vs IVA - F/MF: CUA, ICER \$[REDACTED]² vs BSC	F/RF recommended at same cost per patient as F/F.	6 years and older: \$[REDACTED]²/QALY 12 years and older: \$[REDACTED]²/QALY	would be acceptable if the ICER was between \$60,000-80,000 per QALY gained, and if risk sharing agreements were implemented, including a “pay-for-performance” arrangement. Other Class III: No economic analysis

Source: Table 1.4.2, Table 2.2.1, Table 2.2.2, Table 2.2.3, Table 4.2.11, Table 3.1.32, Table 4.2.3 of the submission; TEZ/IVA Public Summary Document (PSD), March 2019 PBAC meeting; TEZ/IVA PSD, November 2019 PBAC meeting; IVA PSD, July 2013 PBAC meeting; IVA PSD, November 2013 PBAC meeting; IVA PSD, November 2014 PBAC meeting; IVA PSD, November 2015 PBAC meeting; LUM/IVA PSD, July 2019 PBAC meeting.

Abbreviations: BSC = best supportive care; CF = cystic fibrosis; CFTR = Cystic fibrosis transmembrane conductance regulator; CUA = cost-utility analysis; ELX/TEZ/IVA = elxacaftor/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/U = patients with not yet characterised mutation function; ICER = incremental cost effectiveness ratio; ITC = indirect comparison; IVA = ivacaftor; LUM/IVA = lumacaftor and ivacaftor; QALY = quality-adjusted life year; RSA = risk sharing agreement; TEZ/IVA = tezacaftor and ivacaftor; TGA = Therapeutic Goods Administration;

The redacted values correspond to the following ranges:

¹ \$135,000 to < \$155,000

² \$155,000 to < \$255,000

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Name, restriction, manner of administration, form	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
Elxacaftor 100 mg/ tezacaftor 50 mg/ ivacaftor 75 mg film-coated tablets co-packaged with ivacaftor 150 mg film-coated tablets	Pack containing 84 tablets (4-week supply)	-	\$21,375 published price ^a \$[REDACTED] effective price	Trikafta, Vertex Pharmaceuticals (Australia) Pty Ltd
Section 100 (Highly Specialised Drugs Program)				
Authority required				
<i>Treatment phase</i>	<i>Initial treatment</i>			
Treatment criteria:	Must be treated by a specialist respiratory physician with expertise in cystic fibrosis, OR Must be treated in consultation with a specialist respiratory physician with expertise in cystic fibrosis if attendance is not possible due to geographic isolation. AND Must be treated in a centre with expertise in cystic fibrosis, OR Must be treated in consultation with a centre with expertise in cystic fibrosis if attendance is not possible due to geographic isolation.			
Clinical criteria:	Patient must have been diagnosed with cystic fibrosis AND Patient must have at least one F508del mutation <i>in the cystic fibrosis transmembrane conductance regulator (CFTR) gene</i>			

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Section 100 (Highly Specialised Drugs Program)	
Authority required	
	AND The treatment must be the a sole PBS-subsidised <i>cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy</i> disease-modifying therapy for this condition, AND The treatment must be given concomitantly with standard therapy for this condition. AND <i>Patient must have either chronic sinopulmonary disease or gastrointestinal and nutritional abnormalities</i>
Population criteria:	Patients must be 12 years or older.
Prescribing instructions:	Patients receiving PBS-subsidised treatment with this drug must be <i>The patient must be</i> registered in the Australian Cystic Fibrosis Database Registry. Treatment must not be given to a patient who has an acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease in the last 4 weeks prior to commencing this drug. <i>For the purposes of this restriction, PBS subsidised 'CFTR modulator' means ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor and elexacaftor/ tezacaftor/ ivacaftor.</i> The authority application must be in writing and must include: (1) a completed authority prescription form; and (2) a completed Cystic Fibrosis Elexacaftor, Tezacaftor with Ivacaftor Authority Application Supporting Information Form; and (3) a signed patient acknowledgement; or an acknowledgement signed by a parent or authorised guardian, if applicable; and (3) a copy of the pathology report detailing the molecular testing for the patient having at least one F508del mutation on the CFTR gene; and (4) the result of an FEV1 measurement performed within a month before the date of application. Note: FEV1, must be measured in a cystic fibrosis clinic with documented no acute infective exacerbation at the time FEV1 is measured; and (6) evidence that the patient has either chronic sinopulmonary disease or gastrointestinal and nutritional abnormalities; and (5) a copy of a current medication history-current CYP3A4 inhibitors, CYP3A4 inducers and IV antibiotics; and (6) height and weight measurements at the time of application; and (7) a baseline measurement of the number of days of CF-related hospitalisation (including hospital-in-the home) in the previous 12 months.
Administrative advice	<i>No increase in the maximum quantity or number of units may be authorised.</i> <i>No increase in the maximum number of repeats may be authorised</i>

Treatment phase	Continuing treatment
Treatment criteria:	<i>Must be treated by a specialist respiratory physician with expertise in cystic fibrosis, OR</i> <i>Must be treated in consultation with a specialist respiratory physician with expertise in cystic fibrosis if attendance is not possible due to geographic isolation.</i> AND <i>Must be treated in a centre with expertise in cystic fibrosis, OR</i> <i>Must be treated in consultation with a centre with expertise in cystic fibrosis if attendance is not possible due to geographic isolation.</i>

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<i>Treatment phase</i>	<i>Continuing treatment</i>
<i>Clinical criteria:</i>	<i>Patient must have previously received PBS-subsidised treatment with this drug for this condition</i> <i>AND</i> <i>The treatment must be the sole PBS-subsidised cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy for this condition,</i> <i>AND</i> <i>The treatment must be given concomitantly with standard therapy for this condition.</i>
<i>Population criteria:</i>	<i>Patients must be 12 years or older.</i>
<i>Prescribing instructions:</i>	<i>Treatment must not be given to a patient who has an acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease in the last 4 weeks prior to commencing this drug.</i> <i>Patients who have an acute infective exacerbation at the time of assessment for continuing therapy may receive an additional one month's supply in order to enable the assessment to be repeated following resolution of the exacerbation</i> <i>For the purposes of this restriction, PBS subsidised 'CFTR modulator' means ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor and elexacaftor/tezacaftor/ivacaftor.</i> <i>The authority application must be in writing and must include:</i> <i>(1) a completed authority prescription form; and</i> <i>(2) a completed Cystic Fibrosis Elexacaftor, Tezacaftor with Ivacaftor Authority Application Supporting Information Form; and</i> <i>(3) the result of an FEV1 measurement performed within a month before the date of application. Note: FEV1, must be measured in a cystic fibrosis clinic with documented no acute infective exacerbation at the time FEV1 is measured; and</i> <i>(4) current CYP3A4 inhibitors, CYP3A4 inducers and IV antibiotics; and</i> <i>(5) height and weight measurements at the time of application; and</i> <i>(6) the number of days of CF-related hospitalisation (including hospital-in-the home) in the previous 6 months</i>
<i>Administrative advice</i>	<i>No increase in the maximum quantity or number of units may be authorised.</i> <i>No increase in the maximum number of repeats may be authorised</i>

Source: Table 1.4.1, p54; Table 1.4.2, p55 of the submission

Abbreviations: CF= cystic fibrosis; CFTR=cystic fibrosis transmembrane conductance regulator; FEV1=forced expiratory volume in one second; mg = milligram; PBS = Pharmaceutical Benefits Scheme

Note: ^aThe submission used price ex-manufacturer without mark-up, and justified this was appropriate for a Section 100 drug dispensed almost entirely in public hospitals (Manual of Resource Items and their Associated Costs 2009 Section 4.1.2)

- 3.2 The submission requested a Special Pricing Arrangement by proposing a confidential effective price for ELX/TEZ/IVA of \$ [REDACTED] per pack (versus a published DPMQ of \$21,375 per pack. The pre-PBAC response provided a revised effective cost per pack of \$ [REDACTED].
- 3.3 Consistent with all current CFTR modulators, the proposed restriction allows use in all patients irrespective of lung function as measured by ppFEV₁. This is not consistent with the key clinical evidence presented in the submission which included only patients with moderate to mild lung function impairment (classified by percent predicted forced expiratory volume in one second; ppFEV₁ between 40 to 90%).

- 3.4 The requested listing and proposed restriction criteria was for patients with at least one F508del mutation i.e., the F/any population.
- 3.5 The PBAC noted the listings for other CFTR modulators contained advice for dose modifications when combined with specified moderate and strong CYP3A4 inhibitors and a statement that they are not PBS-subsidised in patients receiving a number of specified CYP3A4 inducers. No justification was provided in the submission regarding why similar wording was not included in the proposed listing for ELX/TEZ/IVA.

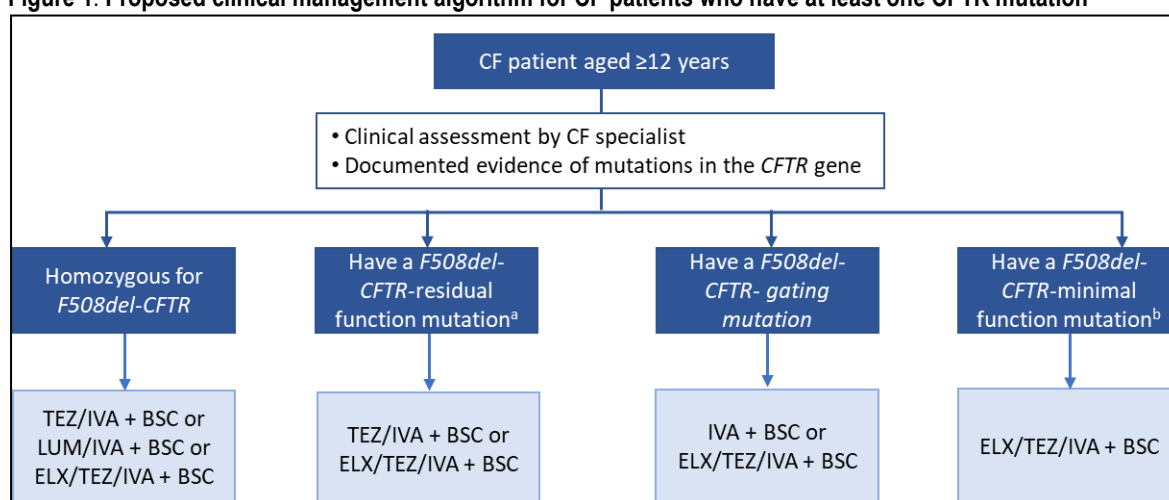
For more detail on the PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 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, pancreatic insufficiency and gastrointestinal malabsorption, frequent pulmonary exacerbations and early death. According to the Australian Cystic Fibrosis Disease Registry (ACFDR 2019 report), the median age of death in Australia in 2017 was 35.6 years.
- 4.2 The most common mutation in CF is the 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. Patients with CF who have 2 alleles that result in complete or near complete loss of CFTR-mediated chloride transport (e.g., F508del, Class I mutations which make no CFTR protein, gating mutations such as G551D) demonstrate severe CF characterised by early onset and relatively rapid disease progression.
- 4.3 Based on registry data from the ACFDR, 53.2% of CF patients aged 12 years and older are homozygous for the F508del mutation in Australia (F/F).
- 4.4 Based on the registry data, 5.5% of CF patients aged 12 years and older with an F508del mutation have a residual function mutation (F/RF). These mutations result in reduced amounts of normal CFTR protein at the cell surface. RF mutations are also associated with a pneumopathy that is delayed in onset and is slower in progression than other forms of CF.
- 4.5 Based on the registry data, 7.5% of CF patients aged 12 years and older with an F508del mutation have a gating mutation (F/G). These mutations result in CFTR proteins that reach the cell surface but are defective and fail to open and close properly, leading to reduced chloride transport.
- 4.6 Based on the registry data, 17.8% of CF patients aged 12 years and older with an F508del mutation have a minimal function mutation (F/MF). These mutations are defined as either: (1) class 1 mutation that results in no CFTR protein, or (2) missense mutations which result in CFTR protein that does not transport chloride and is unresponsive to current PBS-listed CFTR modulators.

- 4.7 The submission stated the remaining cohort of CF patients (16.8%) are those with an F508del mutation and a second CF causing mutation that is unknown and/or has not yet been characterised as gating, RF or MF (F/not yet characterised). The PBAC considered the F/not yet characterised population is not a distinct patient population and for the purpose of calculating phenotype proportions within the F/any population should be considered as either F/MF, F/G or F/RF (paragraph 6.68).
- 4.8 Overall, the proposed treatment algorithms presented by the submission were reasonable (see Figure 1). However, the algorithm was only partly reflected in the evidence presented in the submission which included only patients with moderate to mild lung function impairment.

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



Source: Figure 1.2.1 of the submission.

Abbreviations: BSC = best supportive care; CF = cystic fibrosis; CFTR = CF transmembrane conductance regulator; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; F/F = CF patients homozygous for the F508del-CFTR mutation; F/MF = CF patients heterozygous for the F508del in the CFTR gene with a MF mutation; LUM/IVA = lumacaftor/ivacaftor; MF = minimal function; TEZ/IVA = tezacaftor/ivacaftor

Notes: ^a residual mutation includes P67L, D110H, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T

^b Mutations that 1) produce no CFTR protein production or 2) are unresponsive to CFTR modulators, including TEZ, IVA or a combination of TEZ/IVA, in vitro are classified as "minimal function" mutations. This cohort also includes patients whose second allele is yet to be characterised (F/Not yet characterised patients)

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

5 Comparator

- 5.1 The comparators nominated by the submission were (1) TEZ/IVA for the F/F population (2) TEZ/ IVA for the F/RF population (3) IVA for the F/G population and (4) BSC for the F/MF population. The submission nominated these comparators on the basis that these were the current treatments for the F/F, F/RF and F/G patient groups, while F/MF patients are currently not receiving CFTR directed therapy and therefore receive BSC.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician discussed their experience with ELX/TEZ/IVA and highlighted the significant benefit they have observed in patients being treated with ELX/TEZ/IVA. The clinician noted ELX/TEZ/IVA improved lung function, reduced hospitalisation, improved quality of life and delayed the need for lung transplant in some patients. For patients with residual function mutations, the clinician stated that although the ppFEV₁ gain observed in the clinical trial could be considered small, the benefit of ELX/TEZ/IVA in this population was still clinically important.

Consumer comments

- 6.2 The PBAC noted the input from individuals (2,398), health care professionals (26) and organisations/ groups (3) via the Consumer Comments facility on the PBS website. Of the comments from individuals, the PBAC noted 55 were from individuals living with CF with direct experience of using ELX/TEZ/IVA, 94 were from adults living with CF who would like access to ELX/TEZ/IVA, 281 were from parents of children living with CF who wanted access to ELX/TEZ/IVA for their child. The remainder of the comments were from family members and friends of people living with CF and other interested individuals. Cystic Fibrosis Australia (CFA), an online patient support group and Australian Cystic Fibrosis Centre Directors (ACFCD) provided written input.
- 6.3 The PBAC noted comments from the online patient support group, and those living with, or supporting someone with CF, described a range of benefits of treatment with ELX/TEZ/IVA, including improvement in lung function, reduction in chest infections and exacerbations, weight gain, fewer hospital visits, reduced use of other interventions and improvement in quality of life. A number of comments emphasised the importance of the availability of ELX/TEZ/IVA for CF patients that are not able to access other CFTR modulators.
- 6.4 The PBAC noted the advice received from CFA and ACFCD which were strongly supportive of making ELX/TEZ/IVA available for CF patients as soon as possible. Both groups stated ELX/TEZ/IVA significantly reduces pulmonary exacerbations, reduces hospitalisation and antibiotic use and can prevent permanent, irreversible lung damage.

Clinical trials

- 6.5 The submission was based on the following four key trials:
- (1) two head-to-head trials comparing ELX/TEZ/IVA to TEZ/IVA in the F/F population (Study 103; N = 108 and Study 109; N = 176);
 - (2) one head-to-head trial comparing ELX/TEZ/IVA to TEZ/IVA in the F/RF population (subgroup of Study 104; N = 164);

- (3) one head-to-head trial comparing ELX/TEZ/IVA to IVA in the F/G population (subgroup of Study 104; N =95);
- (4) one head-to-head trial comparing ELX/TEZ/IVA to placebo in F/MF patients (Study 102; N = 405).

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

Table 3: Trials and associated reports presented in the submission

Study ID	Reports
F/F	
Study 103, June 2019 VX17-445-103 NCT03525548	- Clinical Study Report, June 2019: A Phase 3, Randomised, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445 Combination Therapy in Subjects with Cystic Fibrosis Who Are Homozygous for the F508del Mutation (F/F). - Heijerman, H. G. M. et al. (2019). "Efficacy and safety of the elxacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, Phase 3 trial." <i>Lancet</i> 394(10212): 1940-1948. - Heijerman, H. et al. (2019). "Phase 3 efficacy and safety of the ELX/TEZ/IVA triple combination in people with CF homozygous for the F508del mutation." <i>Paediatric Pulmonology</i> 54(Supplement 2): 347. - Majoer, C. et al. (2020). Impact of elxacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) triple combination therapy on health-related quality of life (HRQoL) in people with cystic fibrosis (pwCF) homozygous for F508del (F/F): results from a Phase 3 clinical study. North American Cystic Fibrosis Conference 2020.
Study 109 VX18-445-109 NCT04105972	Clinical Study Report, October 2020: A Phase 3b, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects, Homozygous for F508del
Study 105 Interim Analysis 2, March 2020 VX17-445-105 NCT03525574	- Interim Analysis Summary, March 2020: A Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of VX-445 Combination Therapy in Subjects with Cystic Fibrosis Who Are Homozygous or Heterozygous for the F508del Mutation. - Griese M, et al. Safety and Efficacy of Elxacaftor/Tezacaftor/Ivacaftor for ≥24 Weeks in People with CF and ≥1 F508del Allele: Interim Results of an Open-Label Phase Three Clinical Trial. <i>American journal of respiratory and critical care medicine</i>. 2020.
F/RF, F/G	
Study 104, July 2019 VX18-445-104 NCT04058353	Clinical Study Report, July 2019: A Phase 3, Randomised, Double-blind, Controlled Study Evaluating the Efficacy and Safety of Elxacaftor Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the F508del Mutation and a Gating or Residual Function Mutation (F/G and F/RF Genotypes)
F/MF	
Study 102, July 2019 VX17-445-102 NCT03525444	- Clinical Study Report, July 2019: A Phase 3, Randomised, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445 Combination Therapy in Subjects with Cystic Fibrosis Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF). - Middleton, P. G. et al. (2019). "Elxacaftor-Tezacaftor-Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele." <i>N Engl J Med</i> 381(19): 1809-1819. - Fajac, I. et al. (2020). "Impact of elxacaftor/tezacaftor/ivacaftor triple combination therapy on health-related quality of life in people with cystic fibrosis heterozygous for F508del and a minimal function mutation: results from a Phase 3 clinical study." <i>Journal of Cystic Fibrosis</i> 19(Supplement 2): S118-S119. - Jain, R. et al. (2019). "Phase 3 efficacy and safety of the ELX/TEZ/IVA triple combination in people with CF and F508del/minimal function genotypes." <i>Paediatric Pulmonology</i> 54(Supplement 2): 346-347.
Study 105 Interim Analysis 2, March 2020 VX17-445-105 NCT03525574	- Interim Analysis Summary, March 2020: A Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of VX-445 Combination Therapy in Subjects with Cystic Fibrosis Who Are Homozygous or Heterozygous for the F508del Mutation. - Griese M, et al. Safety and Efficacy of Elxacaftor/Tezacaftor/Ivacaftor for ≥24 Weeks in People with CF and ≥1 F508del Allele: Interim Results of an Open-Label Phase Three Clinical Trial. <i>American journal of respiratory and critical care medicine</i>. 2020.

Source: Table 2.2.1, p60-62; Table 2.2.2, p63; Table 2.2.3, p64 of the submission

6.6 The key features of the direct randomised trials are summarised in Table 4. The studies were randomised, double-blind in design with a low risk of bias.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in the economic model
ELX/TEZ/IVA versus TEZ/IVA (F/F)						
Study 103	108	R, DB, MC 4 weeks ^a	Low	≥ 12 years F/F, 40-90 ppFEV ₁	ppFEV ₁ , CFQ-R Respiratory, BMI, sweat chloride	Not used
Study 109	176	R, DB, MC 24 weeks ^a	Low	≥ 12 years F/F, 40-90 ppFEV ₁	CFQ-R Respiratory, ppFEV ₁ , sweat chloride	ppFEV ₁
ELX/TEZ/IVA versus TEZ/IVA (F/RF) and ivacaftor (F/G)						
Study 104	259 (164 F/RF; 95 F/G)	R, DB, MC 8 weeks ^a	Low	≥ 12 years F/RF or F/G, 40-90 ppFEV ₁	ppFEV ₁ , CFQ-R Respiratory, sweat chloride	ppFEV ₁
ELX/TEZ/IVA versus placebo (F/MF)						
Study 102	405	R, DB, MC 24 weeks	Low	≥ 12 years F/MF, 40-90 ppFEV ₁	ppFEV ₁ , CFQ-R Respiratory, BMI, PEx, sweat chloride	ppFEV ₁ , BMI, PEx

Source: Developed during the evaluation based on p17-20; Table 2.3.1, p68-69; Table 2.4.1, p105-106; Table 2.5.2, p133-134; Table 2.3.8, p78; Table 2.3.9, p78; Table 2.3.10, p79; Table 2.3.11, p79-80; Table 2.3.12, p82-83; Table 2.4.10, p113-114; Table 2.4.11, p115-116; Table 2.5.12, p143; Table 2.5.13, p144; Table 2.5.14, p145 of the submission

Abbreviations: BMI = body mass index; DB = double blind; ELX/TEZ/IVA = elxacaftor/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

a. In Study 103, Study 109, and Study 104, all patients received a 4-week run-in period with TEZA/IVA and were subsequently randomised to ELX/TEZ/IVA or control

6.7 In considering the strength of the clinical evidence presented for each of the populations, the ESC noted the following:

1. There was one study in the F/F population of 24 weeks duration (Study 109) and BMI and PEx were not included as efficacy outcomes. The 4 week study (Study 103) included BMI as an outcome; however, this timeframe is not adequate to support an improvement in nutritional status.
2. Clinical evidence for the F/RF population was from a subgroup of patients in Study 104 for which the follow-up was short (8 weeks), and BMI and PEx were not included as efficacy outcomes.
3. Clinical evidence for the F/G population was from a subgroup of patients in Study 104 for which the follow-up was short (8 weeks), and BMI and PEx were not included as efficacy outcomes.
4. The clinical study for the F/ MF population was of 24 weeks duration and included BMI and PEx as efficacy outcomes.

- 6.8 The pre-PBAC response noted PEx was evaluated as a safety outcome, rather than an efficacy endpoint, in Study 103, Study 109 and Study 104.

Comparative effectiveness

- 6.9 A summary of the results of the absolute change from baseline in ppFEV₁ across the trials is presented in Table 5.

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

Population Trial, follow-up	n/N	Mean baseline (SD)	Mean change (SE)	n/N	Mean baseline (SD)	Mean change (SE)	Mean difference (95% CI)	P-value
1. F/F	ELX/TEZ/IVA			TEZ/IVA				
Study 103, w4	53/55	61.6 (15.4)	10.4 (0.9)	49/52	60.2 (14.4)	0.4 (0.9)	10.0 (7.4, 12.6)	<0.0001
Study 109, w24	NR/87	63.0 (15.1)	11.2 (0.7)	NR/88	64.2 (15.1)	1.0 (0.7)	10.2 (8.2, 12.1)	<0.0001
2. F/RF	ELX/TEZ/IVA			TEZ/IVA				
Study 104 (subgroup), w8	73/82	67.8 (16.3)	2.5 (0.5)	72/82	68.1 (16.4)	0.5 (0.5)	2.0 (0.5, 3.4)^a	0.0093
3. F/G	ELX/TEZ/IVA			IVA				
Study 104 (subgroup), w8	42/50	66.0 (14.8)	5.8 (0.8)	42/45	68.1 (16.6)	0.1 (0.9)	5.8 (3.5, 8.0)^a	<0.0001
4. F/MF	ELX/TEZ/IVA			Placebo				
Study 102, w24	196/200	61.6 (15.0)	13.9 (0.6)	203/203	61.3 (15.5)	-0.4 (0.5)	14.3 (12.7, 15.8)	<0.0001

Source: Table 2.3.13, p85; Table 2.3.14, p86; Table 2.4.13, p118; Table 2.5.15, p14, Table 2.5.22, pg156 of the submission
Abbreviations: CI = confidence interval; ELX/TEZ/IVA = elxacaftor/tezacaftor/ivacaftor; 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; IVA = ivacaftor; n = number of patients with event; N = total patients in group; NR = not reported; ppFEV₁ = percent predicted forced expiratory volume in one second; SD = standard deviation; SE = standard error; w = week; Sub = subpopulation; TEZ/IVA = tezacaftor and ivacaftor

Bold indicates statistically significant difference

Note: ^a 3.5 (95% CI: 2.2, 4.7) in the ITT population

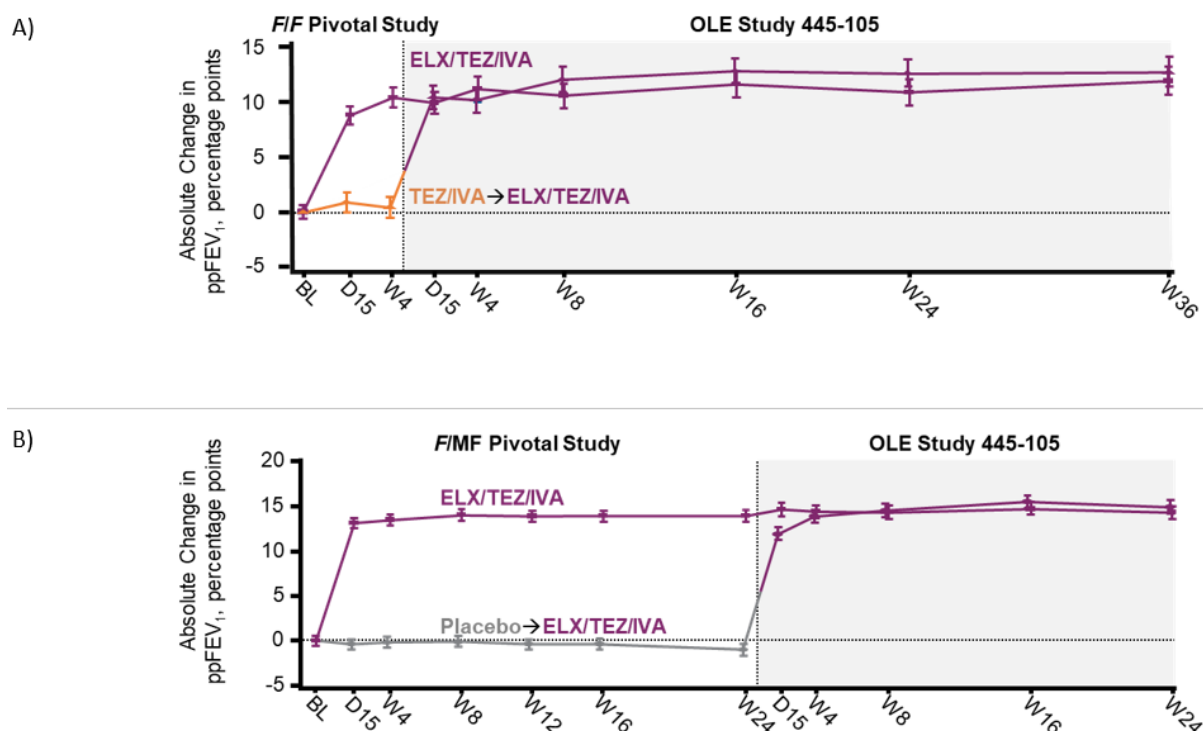
- 6.10 Results from the trials indicated the mean treatment difference compared to the control arm for the change from baseline in ppFEV₁ was statistically significant with an absolute change of (1) 10.0 (95% CI: 7.4, 12.6) at 4 weeks and 10.2 (95% CI: 8.2, 12.1) at 24 weeks in the F/F population (2) 2.0 (95% CI: 0.5, 3.4) at 8 weeks in the F/RF population; (3) 5.8 (95% CI: 3.5, 8.0) at 8 weeks in the F/G population; and (4) 14.3 (95% CI: 12.7, 15.8) at 24 weeks in the F/MF population.
- 6.11 The evaluation noted the improvement in ppFEV₁ in both F/F studies (vs TEZ/IVA) and the F/MF study (vs BSC) exceeded a minimum clinically important difference (MCID) for ppFEV₁ of an absolute change of 10% that was previously considered by the PBAC (paragraph 6.10, LUM/IVA Public Summary Document (PSD), March 2016 PBAC meeting; Section 12, ivacaftor, PSD, July 2013 PBAC meeting). The ESC recalled the sponsor had previously stated that the objective of CF treatment is to maintain lung function and the PBAC had acknowledged that maintaining or slowing decline in lung function was the main aim of CF treatment (paragraph 6.13, LUM/IVA PSD, July 2018 PBAC meeting). The ESC recalled the PBAC had previously considered that, in addition to ppFEV₁, outcomes such as increase in weight (which may support an improvement in nutritional status) and a reduction in the number of pulmonary

exacerbations (including exacerbations requiring hospitalisations and/or intravenous antibiotics) are clinically important outcomes (paragraph 7.7, LUM/IVA PSD, March 2016 PBAC meeting).

- 6.12 The results were based on a relatively short period within the clinical trials. The submission substantiated longer-term results of response duration from an interim analysis of Study 105 (rollover study for Study 103 (F/F) and Study 102 (F/MF) with a planned follow-up of 96 weeks); see Figure 3. The interim analysis (data cut-off 31 October 2019) from Study 105 presented data from a total follow-up of 40 weeks for F/F and 48 weeks for F/MF. The results suggest that ppFEV₁ of patients receiving ELX/TEZ/IVA continued to remain stable over periods of up to 48 weeks. The ESC noted the primary completion date for Study 105 was September 2020. The ESC noted there are additional studies underway that may provide longer term data for ELX/TEZ/IVA¹. The ESC recalled the PBAC had previously considered clinical data from extension studies with up to 96 weeks follow up for LUMA/IVA (paragraph 6.9, LUM/IVA PSD, July 2018 PBAC meeting) and up to 48 weeks follow up for TEZ/IVA (paragraph 6.11, TEZ/IVA PSD, March 2019 PBAC meeting).

¹ <https://clinicaltrials.gov/ct2/show/NCT04362761> and <https://clinicaltrials.gov/ct2/show/NCT04058366>

Figure 2: Absolute change from Baseline in ppFEV₁ by Visit in A) F/F patients (Study 103/OL-FAS Study 105) and B) F/MF patients (Study 102/OL-FAS Study 105)



Source: Figure ES.1 of the submission

Abbreviations: BL = baseline; D = day; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; FAS = Full Analysis Set; 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; MMRM = mixed-effects model for repeated measures; ppFEV₁ = percent predicted forced expiratory in one second; OL, open-label; TEZ/IVA = tezacaftor/ivacaftor; W = week

A summary of the mean treatment difference compared to the control arm for absolute change from baseline in the CFQ-R Respiratory Domain results across the trials is presented in Table 6.

Table 6: Results of absolute change from baseline in CFQ-R Respiratory Domain score across the trials

Population Trial, follow-up	n/N	Mean baseline (SD)	Mean change (SE)	n/N	Mean baseline (SD)	Mean change (SE)	Mean difference (95% CI)	P-value
1. F/F	ELX/TEZ/IVA			TEZ/IVA				
Study 103, w4	55/55	70.6 (16.2)	16.0 (2.0)	52/52	72.6 (17.9)	-1.4 (2.0)	17.4 (11.8, 23.0)	<0.0001
Study 109, w24	NR/87	71.2 (19.6)	17.1 (1.5)	NR/88	73.1 (17.6)	1.2 (1.5)	15.9 (11.7, 20.1)	<0.0001
2. F/Rf	ELX/TEZ/IVA			TEZ/IVA				
Study 104 (subgroup), w8	81/82	76.7 (16.9)	10.4 (1.6)	81/81	78.1 (14.7)	1.9 (1.6)	8.5 (4.0, 13.1)^a	0.0003
3. F/G	ELX/TEZ/IVA			IVA				
Study 104 (subgroup), w8	49/50	76.3 (16.4)	10.2 (1.8)	45/45	75.8 (17.6)	1.3 (1.9)	8.9 (3.8, 14.0)^a	0.0008
4. F/MF	ELX/TEZ/IVA			Placebo				
Study 102, w24	200/200	68.3 (16.9)	17.5 (1.0)	203/203	70.0 (17.8)	-2.7 (1.0)	20.2 (17.5, 23.0)	<0.0001

Source: Table 2.3.13, p85; Table 2.3.14, p86; Table 2.4.13, p118; Table 2.5.15, p147 of the submission

Abbreviations: CI = confidence interval; ELX/TEZ/IVA = elxacaftor/tezacaftor/ivacaftor; 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; IVA = ivacaftor; n = number of patients with event; N = total patients in group; NR = not reported; ppFEV₁ = percent predicted forced expiratory volume in one second; SD = standard deviation; SE = standard error; w = week; Sub = subpopulation; TEZ/IVA = tezacaftor and ivacaftor

Bold indicates statistically significant difference

^a 8.7 (95% CI: 5.3, 12.1) in the ITT population

- 6.13 Results from all of the trials indicated the mean treatment difference compared to the control arm for the change from baseline in the CFQ-R Respiratory Domain score was statistically significant with an absolute change of (1) 17.4 (95% CI: 11.8, 23.0) at 4 weeks and 15.9 (95% CI: 11.7, 20.1) at 24 weeks in the F/F population; (2) 8.5 (95% CI: 4.0, 13.1) at 8 weeks in the F/Rf population; (3) 8.9 (95% CI: 3.8, 14.0) at 8 weeks in the F/G population and (4) 20.2 (95% CI: 17.5, 23.0) at 24 weeks in the F/MF population.
- 6.14 A summary of the absolute change from baseline in sweat chloride across the trials is presented in Table 7.

Table 7: Results of absolute change in sweat chloride from baseline across the trials

Population Trial, follow-up	n/N	Mean baseline (SD)	Mean change (SE)	n/N	Mean baseline (SD)	Mean change (SE)	Mean difference (95% CI)	P-value
1. F/F	ELX/TEZ/IVA			TEZ/IVA				
Study 103, w4	54/55	91.4 (11.0)	-43.4 (1.7)	48/52	90.0 (12.3)	1.7 (1.8)	-45.1 (-50.1, -40.1)	<0.0001
Study 109, w24	NR/87	89.0 (12.2)	-46.2 (1.3)	NR/88	89.9 (11.7)	-3.4 (1.2)	-42.8 (-46.2, -39.3)	<0.0001
2. F/RF	ELX/TEZ/IVA			TEZ/IVA				
Study 104 (subgroup), w8	72/82	64.7 (27.9)	-23.1 (1.3)	75/81	61.4 (27.3)	1.7 (1.3)	-24.8^a (-28.4, -21.2)	<0.0001
3. F/G	ELX/TEZ/IVA			IVA				
Study 104 (subgroup), w8	43/50	50.9 (23.3)	-21.8 (2.0)	44/45	47.6 (19.1)	-1.8 (2.0)	-20.0^a (-25.4, -14.6)	<0.0001
4. F/MF	ELX/TEZ/IVA			Placebo				
Study 102, w24	199/200	102.3 (11.9)	-42.2 (0.9)	201/203	102.9 (9.8)	-0.4 (0.9)	-41.8 (-44.4, -39.3)	<0.0001

Source: Table 2.3.17, p90; Table 2.3.18, p92; Table 2.4.16, 121; Table 2.5.16, p148 of the submission.

Abbreviations: CI = confidence interval; 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; n = number of patients with event; N = total patients in group; NR = not reported; SD = standard deviation; SE = standard error; w = week; Sub = subpopulation

Bold indicates statistically significant difference

^a -23.1 (95% CI: -26.1, -20.1) in the ITT population

- 6.15 Results from all of the trials indicated a statistically significant improvement in the absolute change from baseline in sweat chloride, with an absolute change of (1) -45.1 (95% CI: -50.1, -40.1) at 4 weeks, -42.8 (95% CI: -46.2, -39.3) at 24 weeks in the F/F population; (2) -24.8 (-28.4, -21.2) at 8 weeks in the F/RF population; (3) -20.0 (95% CI: -25.4, -14.6) at 8 weeks in the F/G population and (4) -41.8 (95% CI: -44.4, -39.3) at 24 weeks in the F/MF population.
- 6.16 Study 103 (F/F population) and Study 102 (F/MF population) reported improvement in body mass index (BMI) outcomes (Table 8). Both trials indicated a statistically significant improvement in the absolute change in BMI from baseline, with a change of 0.60 (95% CI: 0.41, 0.79) in the F/F population through Week 4 and a change of 1.04 (95% CI: 0.85, 1.23) in the F/MF population through Week 24. The PBAC previously noted that changes in BMI observed over short durations (e.g. 8 weeks) might not indicate an improvement in nutritional status (paragraph 6.13, TEZ/IVA PSD, March 2019 PBAC meeting; RF) but that improvements beyond 24 weeks may indicate clinical effectiveness (paragraph 7.6, LUM/IVA PSD, July 2017 PBAC meeting).

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

Population Trial, follow-up	n/N	Mean baseline (SD)	Mean change (SE)	n/N	Mean baseline (SD)	Mean change (SE)	Mean difference (95% CI)	P-value
F/F		ELX/TEZ/IVA			TEZ/IVA			
Study 103, w4	55/55	21.75 (3.19)	0.53 (0.07)	52/52	21.88 (4.12)	-0.07 (0.07)	0.60 (0.41, 0.79)	<0.0001
F/MF		ELX/TEZ/IVA			Placebo			
Study 102, w24	198/200	21.49 (3.07)	1.13 (0.07)	202/203	21.13 (3.14)	0.09 (0.07)	1.04 (0.85, 1.23)	<0.0001

Source: Developed during the evaluation based on Table 2.3.13, p85; Table 2.3.14, p86; Table 2.4.13, p118; Table 2.5.15, p147 of the submission

Abbreviations: BMI = body mass index; 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; N = total patients in group SD = standard deviation; SE = standard error; w = week

Bold indicates statistically significant difference

- 6.17 Only Study 102 (F/MF population) reported pulmonary exacerbations (PE_x) as an efficacy outcome (Table 9). The results from the trial indicated that ELX/TEZ/IVA resulted in a statistically significant reduction in PE_x through Week 24, with a PE_x rate that was 63% lower in the ELX/TEZ/IVA group than the placebo group (rate ratio = 0.37; 95% CI: 0.25, 0.55; P<0.0001). No evidence was presented comparing ELX/TEZ/IVA with TEZ/IVA (for the F/F and F/RF populations) or with IVA (for the F/G populations) for the PE_x outcome (infective PE_x as an adverse event is discussed in paragraphs 6.21 and 6.22). The ESC recalled the sponsor had previously stated that PE_x are the primary cause of morbidity in CF and associated with a permanent decline in lung function (paragraph 6.17, LUM/IVA PSD, July 2018 PBAC meeting). The PBAC acknowledged that a reduction in PE_x is an important clinical outcome for CF patients; however, the PBAC considered that there was still uncertainty around the longer term impact of LUM/IVA on PE_x (beyond 96 weeks) (paragraph 6.17, LUM/IVA PSD, July 2018 PBAC meeting).

Table 9: Results of estimated event rate per year for PE_x in Study 102 (F/MF population)

Population Trial, follow-up	Event rate per year		Rate ratio (95% CI)	P-value
F/MF	ELX/TEZ/IVA	BSC		
Study 102, w24	0.37	0.98	0.37 (0.25, 0.55)	<0.0001

Source: Developed during the evaluation based on Table 2.4.15, 119 of the submission

Abbreviations: CI = confidence interval; F/MF = CF patient heterozygous for the F508del in the CFTR gene with a minimal function mutation; PE_x = pulmonary exacerbation; w = week

Notes: PE_x was defined as any new or change in antibiotic therapy (IV, inhaled, or oral) for ≥4 sinopulmonary signs/symptoms. PE_x analysis period duration in years as the offset. The event rate was calculated based on 336 days (48 weeks) in a year; Bold indicates statistically significant difference

- 6.18 In addition to the lack of efficacy data for BMI and PE_x, the main issue for the clinical efficacy data is that they were based on a short duration of follow-up (4 and 24 weeks for F/F population, 8 weeks for F/RF and F/G populations and 24 weeks for the F/MF population).
- 6.19 The PBAC has previously considered submissions presenting comparative evidence based on 8 to 24 weeks in duration in the same setting and considered these to be of a short duration of follow-up and that it was unknown whether such treatment effect in improvement of ppFEV₁ would be maintained longer term or whether the

treatment effect would translate to a gain in life expectancy (paragraph 7.5, TEZ/IVA PSD, March 2019 PBAC meeting; RF).

- 6.20 The patients included in the clinical trials had mild or moderate lung dysfunction (ppFEV₁ 40 to 90%). Compared with the trials, CF patients aged 12 years and older in Australia appear to have better lung function (ACFDR 2019 report; 2017 data); mean ppFEV₁ in Australian CF patients ranges from 74.2 to 80.1% (depending on the population) versus 60.9 to 67.9% in the trials. The ESC noted 28% of Australian patients were classified as having a normal lung function (ppFEV₁ ≥ 90) versus 3% in the trials (Table 10). The Pre-Sub-Committee Response (PSCR) stated that for CF patients with normal lung function (ppFEV₁ > 90%), other manifestations of CF disease will be present such as pancreatic insufficiency and structural lung damage, and in these patients, pulmonary exacerbations and severe lung infections will lead to reduction in lung function. The ESC noted there was no clinical evidence presented in patients with normal lung function. The ESC noted results from a subgroup analysis from Study 103 suggest that those with higher ppFEV₁ at baseline may experience less benefit in improving ppFEV₁ from treatment (6.3; 95% CI: 2.3, 10.4 in ppFEV₁ ≥ 70 versus 11.2; 95% CI: 8.0, 14.4 in ppFEV₁ < 70 based on Study 103). The ESC further noted it was unknown if treatment with ELX/TEZ/IVA resulted in improved outcomes compared with TEZ/IVA in patients with normal lung function.

Table 10: Comparing generated baseline ppFEV₁ distribution by age groups in the model to Australian data

	<40% (Severe)		≥40%-70% (Moderate)		≥70%-90% (Mild)		≥90% (Normal)	
	Model	Australia	Model	Australia	Model	Australia	Model	Australia
12-17 years	5%	2%	46%	16%	45%	30%	4%	52%
18-29 years	8%	8%	64%	34%	27%	32%	1%	26%
30+ years	11%	15%	71%	44%	18%	29%	1%	11%
Total	8%	9%	62%	32%	28%	30%	2%	28%

Source: Developed during the evaluation based on 'PatientProfiles' in the economic model worksheet; Table 3.5, p21 of ACFDR 2017
Abbreviations: ppFEV₁ = percent predicted forced expiratory volume in one second

Comparative harms

- 6.21 A summary of the adverse events for ELX/TEZ/IVA versus TEZ/IVA for the F/F population in Study 103 and Study 109 is presented in Table 11. The pre-PBAC response reported infective PEx adverse events occurred less frequently in the ELX/TEZ/IVA group than the TEZ/IVA group (1.8% vs 11.5% in Study 103; 11.5% vs 40.9% in Study 109).

Table 11: Overview of AEs in Study 103 (4 weeks) and Study 109 (24 weeks), Safety Set

Category, n (%)	Study 103 (F/F population)		RD (95% CI)	Study 109 (F/F population)		RD (95% CI)
	ELX/TEZ/IVA N=55	TEZ/IVA N=52		ELX/TEZ/IVA N=87	TEZ/IVA N=88	
Any AEs	32 (58.2)	33 (63.5)	-0.05 (-0.24, 0.13)	77 (88.5)	81 (92.0)	-0.04 (-0.12, 0.05)
AEs by strongest relationship						
Not related	16 (29.1)	19 (36.5)	-0.09 (-0.27, 0.08)	20 (23.0)	27 (30.7)	-0.08 (-0.21, 0.05)
Unlikely related	4 (7.3)	5 (9.6)	-0.02 (-0.13, 0.08)	19 (21.8)	29 (33.0)	-0.11 (-0.24, 0.02)
Possibly related	11 (20.0)	8 (15.4)	0.05 (-0.10, 0.19)	30 (34.5)	24 (27.3)	0.07 (-0.06, 0.21)
Related	1 (1.8)	1 (1.9)	0.00 (-0.05, 0.05)	8 (9.2)	1 (1.1)	0.08 (0.02, 0.15)
AEs by maximum severity						
Mild	23 (41.8)	21 (40.4)	0.01 (-0.17, 0.20)	48 (55.2)	46 (52.3)	0.03 (-0.12, 0.18)
Moderate	9 (16.4)	11 (21.2)	-0.05 (-0.20, 0.10)	22 (25.3)	28 (31.8)	-0.07 (-0.20, 0.07)
Severe	0	1 (1.9)	-0.02 (-0.06, 0.02)	7 (8.0)	7 (8.0)	0.00 (-0.08, 0.08)
Life-threatening	0	0	0.00 (0.00, 0.00)	0	0	0.00 (0.00, 0.00)
AEs leading to study drug discontinuation						
	0	0	0.00 (0.00, 0.00)	1 (1.1)	2 (2.3)	-0.01 (-0.05, 0.03)
AEs leading to study drug interruption						
	0	0	0.00 (0.00, 0.00)	2 (2.3)	1 (1.1)	0.01 (-0.03, 0.05)
Grade 3/4 AEs	0 (0.0)	1 (1.9)	-0.02 (-0.06, 0.02)	7 (8.0)	7 (8.0)	0.00 (-0.08, 0.08)
Related AEs^a	12 (21.8)	9 (17.3)	0.05 (-0.11, 0.20)	8 (9.2)	1 (1.1)	0.08 (0.02, 0.15)
SAEs	2 (3.6)	1 (1.9)	0.02 (-0.05, 0.08)	5 (5.7)	14 (15.9)	-0.10 (-0.19, -0.01)
Related SAEs^a	1 (1.8)	0	0.02 (-0.02, 0.05)	2 (2.3)	2 (2.3)	0.00 (-0.04, 0.04)

Source: Developed during the evaluation based on Table 2.3.22, p99-100 of the submission

Abbreviations: AE = adverse event; CI = confidence interval; ELX/TEZ/IVA = elxacaftor/tezacaftor/ivacaftor; RD = risk difference; SAE = serious adverse event; TEZ/IVA = tezacaftor/ivacaftor

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.

^a When summarising number of subjects with related (serious) AEs, AEs with relationship of related, possibly related, and missing were counted.

Bold indicates statistical significance.

6.22 A summary of the adverse events for ELX/TEZ/IVA versus TEZ/IVA in the F/RF population and IVA in the F/G population in Study 104 and ELX/TEZ/IVA versus placebo in the F/MF population in Study 102 are presented in Table 12. The pre-PBAC response reported infective PEx adverse events occurred less frequently in the ELX/TEZ/IVA group compared to the TEZ/IVA or IVA group (2.3% vs 10.3% in Study 104).

Table 12: Overview of AEs in Study 104 and Study 102, Safety Set

Category, n (%)	Study 104 (F/Rf and F/G population)		RD (95% CI)	Study 102 (F/MF population)		RD (95% CI)
	ELX/TEZ/IVA N=132	Control N=126		ELX/TEZ/IVA N=202	Placebo N=201	
Any AEs	88 (66.7)	83 (65.9)	0.01 (-0.11, 0.12)	188 (93.1)	193 (96.0)	-0.03 (-0.07, 0.01)
AEs by strongest relationship						
Not related	35 (26.5)	45 (35.7)	-0.09 (-0.20, 0.02)	53 (26.2)	83 (41.3)	-0.15 (-0.24, -0.06)
Unlikely related	21 (15.9)	16 (12.7)	0.03 (-0.05, 0.12)	39 (19.3)	58 (28.9)	-0.10 (-0.18, -0.01)
Possibly related	30 (22.7)	22 (17.5)	0.05 (-0.05, 0.15)	86 (42.6)	46 (22.9)	0.20 (0.11, 0.29)
Related	2 (1.5)	0	0.02 (-0.01, 0.04)	10 (5.0)	6 (3.0)	0.02 (-0.02, 0.06)
AEs by maximum severity						
Mild	58 (43.9)	50 (39.7)	-0.08 (-0.08, 0.16)	67 (33.2)	53 (26.4)	0.07 (-0.02, 0.16)
Moderate	25 (18.9)	29 (23.0)	-0.14 (-0.14, 0.06)	102 (50.5)	125 (62.2)	-0.12 (-0.21, -0.02)
Severe	5 (3.8)	4 (3.2)	-0.04 (-0.04, 0.05)	19 (9.4)	14 (7.0)	0.02 (-0.03, 0.08)
Life-threatening	0	0	0.00 (0.00, 0.00)	0	1 (0.5)	0.00 (-0.01, 0.00)
AEs leading to study drug discontinuation						
	1 (0.8)	2 (1.6)	-0.03 (-0.03, 0.02)	2 (1.0)	0	0.01 (0.00, 0.02)
AEs leading to study drug interruption						
	5 (3.8)	3 (2.4)	-0.03 (-0.03, 0.06)	19 (9.4)	10 (5.0)	0.04 (-0.01, 0.09)
Grade 3/4 AEs						
	5 (3.8)	4 (3.2)	-0.04 (-0.04, 0.05)	19 (9.4)	15 (7.5)	0.02 (-0.03, 0.07)
Related AEs^a						
	32 (24.2)	22 (17.5)	-0.03 (-0.03, 0.17)	96 (47.5)	52 (25.9)	0.22 (0.12, 0.31)
SAEs						
	5 (3.8)	11 (8.7)	-0.11 (-0.11, 0.01)	28 (13.9)	42 (20.9)	-0.07 (-0.14, 0.00)
Related SAEs^a						
	0	2 (1.6)	-0.04 (-0.04, 0.01)	6 (3.0)	2 (1.0)	0.02 (-0.01, 0.05)

Source: Developed during the evaluation based on Table 2.5.20, p154; Table 2.4.20, p127-128 of the submission

Abbreviations: AE = adverse event; CI = confidence interval; ELX/TEZ/IVA = elxacaftor/tezacaftor/ivacaftor; RD = risk difference; SAE = serious adverse event

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.

^a When summarising number of subjects with related (serious) AEs, AEs with relationship of related, possibly related, and missing were counted.

Bold indicates statistical significance.

6.23 The safety data from the trials indicated that ELX/TEZ/IVA appeared to be generally well tolerated with a comparable side-effect profile to the comparators throughout the trial period.

Benefits/harms

6.24 A summary of the comparative benefits and harms for ELX/TEZ/IVA versus the comparators is presented in Table 13. Results for the F/F population are from Study 109 which presents results following 24 weeks of treatment; Study 103 reported 4-week results only.

Table 13: Summary of comparative benefits and harms for ELX/TEZ/IVA versus comparators

Benefits: Change from baseline in absolute change in ppFEV ₁							
Population Trial, follow up	Treatment			Comparator			Mean difference (95% CI)
	N	Mean change	SE	N	Mean change	SE	
F/F	ELX/TEZ/IVA			TEZ/IVA			
Study 109, w24	87	11.2	0.7	88	1.0	0.7	10.2 (8.2, 12.1)
F/RF	ELX/TEZ/IVA			TEZ/IVA			
Study 104 (subgroup), w8	82	2.5	0.5	82	0.5	0.5	2.0 (0.5, 3.4)
F/G	ELX/TEZ/IVA			IVA			
Study 104 (subgroup), w8	50	5.8	0.8	45	0.1	0.9	5.8 (3.5, 8.0)
F/MF	ELX/TEZ/IVA			BSC			
Study 102, w24	200	13.9	0.6	203	-0.4	0.5	14.3 (12.7, 15.8)
Harms							
	Treatment	Comparator	RR (95% CI)	Event rate/100 patients		RD (95% CI)	
				ELX/TEZ/IVA	Comparators		
Patients with Grade 3 or Grade 4 AE							
F/F	ELX/TEZ/IV A	TEZ/IVA		ELX/TEZ/IVA	TEZ/IVA		
Study 109, w24	7/87	7/88	1.01 (0.37, 2.76)	8.0	8.0	0.00 (-0.08, 0.08)	
F/RF and F/G	ELX/TEZ/IV A	TEZ/IVA and IVA		ELX/TEZ/IVA	TEZ/IVA and IVA		
Study 104, w8	5/132	4/126	1.19 (0.33, 4.34)	3.8	3.2	-0.04 (-0.04, 0.05)	
F/MF	ELX/TEZ/IV A	BSC		ELX/TEZ/IVA	BSC		
Study 102, w24	19/202	15/201	1.26 (0.66, 2.41)	9.4	7.5	0.02 (-0.03, 0.07)	
Related AE							
F/F	ELX/TEZ/IV A	TEZ/IVA		ELX/TEZ/IVA	TEZ/IVA		
Study 109, w24	8/87	1/88	8.09 (1.03, 63.34)	9.2	1.1	0.08 (0.02, 0.15)	
F/RF and F/G	ELX/TEZ/IV A	TEZ/IVA and IVA		ELX/TEZ/IVA	TEZ/IVA and IVA		
Study 104, w8	0/132	2/126	NA	0.0	1.6	-0.04 (-0.04, 0.01)	
F/MF	ELX/TEZ/IV A	BSC		ELX/TEZ/IVA	BSC		
Study 102, w24	6/202	2/201	2.99 (0.61, 14.61)	3.0	1.0	0.02 (-0.01, 0.05)	

Source: Developed during the evaluation based on Table 2.3.22, p99-100; Table 2.5.20, p154; Table 2.4.20, p127-128; Table 2.4.15, 119 of the submission

Abbreviations: AE = adverse event; CI = confidence interval; ELX/TEZ/IVA = elxacaftor/tezacaftor/ivacaftor; 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; RD = risk difference; RR = relative risk; SE = standard error

Note: Bold indicates statistical significance, w=weeks.

6.25 On the basis of direct evidence from trials presented in the submission:

- The F/F population treated with ELX/TEZ/IVA achieved approximately 10.2% increase in lung capacity (as measured by ppFEV₁) compared with TEZ/IVA at 24 weeks.
- The F/RF population treated with ELX/TEZ/IVA achieved approximately 2% increase in lung capacity (as measured by ppFEV₁) compared with TEZ/IVA at 8

weeks. This is less than the increase in lung capacity that the PBAC has previously considered to be clinically meaningful (i.e., MCID of 10%).

- The F/G population treated with ELX/TEZ/IVA achieved approximately 5.8% increase in lung capacity (as measured by ppFEV₁) compared with IVA at 8 weeks. This is less than the increase in lung capacity that the PBAC has previously considered to be clinically meaningful (i.e., MCID of 10%).
- F/MF patients treated with ELX/TEZ/IVA achieved approximately 14.3% increase in lung capacity (as measured by ppFEV₁) compared with BSC at 24 weeks.

- 6.26 On the basis of direct evidence from trials presented in the submission, patients treated with ELX/TEZ/IVA have no increase in the overall likelihood of harm compared with TEZ/IVA, IVA, or BSC over a period of up to 24 weeks.

Clinical claim

- 6.27 For the F/F population, the submission described ELX/TEZ/IVA as superior in terms of effectiveness compared to TEZ/IVA. The ESC considered the evidence presented indicated a significant improvement in outcomes of ppFEV₁, CFQ-R Respiratory Domain score and sweat chloride at 4 weeks and 24 weeks versus TEZ/IVA. The ESC noted the improvement in ppFEV₁ was greater than the MCID of 10% at 4 weeks and 24 weeks. The BMI outcome for F/F patients was based on a short duration of treatment in Study 103 (4 weeks) and the clinical significance of this over the longer term is uncertain. The PBAC noted infective PEx was collected as a safety outcome.
- 6.28 For the F/RF population, the submission described ELX/TEZ/IVA as superior in terms of effectiveness compared to TEZ/IVA. The ESC noted the evidence presented for outcomes of ppFEV₁, CFQ-R Respiratory Domain score and sweat chloride were based on a short duration of treatment (8 weeks). The ESC noted the improvement in ppFEV₁ (2.0%) was described by the TGA Delegate as small and was less than the 10% MCID previously considered by the PBAC, and that there was no evidence presented for BMI and PEx outcomes, and thus considered the claim of superior effectiveness was not adequately supported. The PBAC noted infective PEx was collected as a safety outcome.
- 6.29 For F/G patients, the submission described ELX/TEZ/IVA as superior in terms of effectiveness compared to IVA. The ESC noted the evidence presented for outcomes of ppFEV₁, CFQ-R Respiratory Domain score and sweat chloride were based on a short duration of treatment (8 weeks). The ESC noted the improvement in ppFEV₁ (5.8%) was described by the TGA Delegate as small and was less than the 10% MCID previously considered by the PBAC, and that there was no evidence presented for BMI and PEx, and thus considered the claim of superior effectiveness was not adequately supported. The PBAC noted infective PEx was collected as a safety outcome.
- 6.30 The pre-PBAC response stated the claim of superior effectiveness for the F/RF and F/G populations is strongly supported by the results of Study 104 and noted the ACM conclusion that ELX/TEZ/IVA demonstrated significant and meaningful benefits in all

primary and secondary endpoints in the clinical trial. The pre-PBAC response stated the PBAC had previously approved other CFTR modulators which demonstrate similar improvements in ppFEV₁. The PBAC recalled it had previously approved other CFTR modulators with a lower ppFEV₁ benefit; however, that was in the context of clinical trials with longer follow-up (and noted Study 104 was an 8 week trial) and supported by benefits in other relevant clinical outcomes such as BMI and PEx.

- 6.31 For F/MF, the submission described ELX/TEZ/IVA as superior in terms of effectiveness compared to BSC. The ESC considered the evidence presented indicated a significant improvement in all key outcomes including ppFEV₁, CFQ-R Respiratory Domain score, sweat chloride, BMI, and PEx at 24 weeks versus BSC. The ESC noted the improvement in ppFEV₁ was greater than the MCID of 10%.
- 6.32 The submission described ELX/TEZ/IVA as comparable in terms of safety compared to TEZ/IVA (F/F, F/RF populations), IVA (F/G population) and BSC (F/MF population). The ESC considered the claim of comparable safety appeared to be adequately supported across all populations, noting the short duration of treatment for the F/RF and F/G populations. The ESC recalled the PBAC had previously considered that the claim of non-inferior comparative safety of LUM/IVA versus BSC was not adequately supported by data from the PROGRESS study (paragraph 6.40, LUM/IVA PSD, July 2017 PBAC meeting) which provided data for up to 96 weeks of follow up.
- 6.33 The ESC noted the clinical claim in the F/not yet characterised population was based on the assumption that the efficacy and safety of ELX/TEZ/IVA in the F/MF group is representative of the F/not yet characterised population.
- 6.34 The PBAC considered that the claim of superior comparative effectiveness was reasonable for the F/F (vs TEZ/IVA) and F/MF (vs BSC) populations over 24 weeks, but was not adequately supported for the F/RF (vs TEZ/IVA) and F/G (vs IVA) populations.
- 6.35 The PBAC considered that the claim of non-inferior comparative safety (vs TEZ/IVA, BSC and IVA) was reasonable but this was based on up to 24 weeks of clinical data.

Economic analysis

- 6.36 The submission presented separate economic evaluations for each population.
 - 1. A modelled economic evaluation was presented for the F/F population comparing TEZ/IVA with BSC and then ELX/TEZ/IVA with TEZ/IVA. The structure of the model was similar to that considered by the PBAC for previous CFTR directed therapies, including use of the Irish CF registry to model the BSC arm and the Liou et al algorithm to model the relationship between surrogate markers and mortality. The comparison of TEZ/IVA vs BSC was informed by the EVOLVE trial. The comparison of ELX/TEZ/IVA with TEZ/IVA was informed by Study 109. To support this approach the submission presented an indirect treatment comparison (ITC) of the relevant studies. The ESC noted the structure of the model necessitated a BSC arm be modelled as well as the comparator (TEZ/IVA) which required the use of data beyond the head to head trial. This reduced the

generalisability and increased the uncertainty of the model results. The PSCR stated that using the ITC results to populate the models yielded almost identical input values as seen in the head-to-head trials (using ppFEV₁ as an example, for the F/F population the modelled for incremental benefit was 10.2 which was identical to that observed in the head-to-trial).

2. A modelled economic evaluation was presented for the F/RF population comparing TEZ/IVA with BSC and then ELX/TEZ/IVA with TEZ/IVA using the same approach as for the F/F population. The comparison of TEZ/IVA vs BSC was informed by the EXPAND trial. The comparison of ELX/TEZ/IVA with TEZ/IVA was informed by a subgroup of Study 104. To support this approach the submission presented an ITC of the relevant studies. The ESC noted a cost-effectiveness analysis is only appropriate if the claim of superior effectiveness is accepted.
 3. A cost comparison was presented for the F/G population comparing ELX/TEZ/IVA and IVA. The comparison was based on a subgroup of Study 104.
 4. A modelled economic evaluation was presented for the F/MF population comparing ELX/TEZ/IVA with BSC using the same approach as for the F/F population. The comparison was based on a head to head trial, Study 102.
- 6.37 The key components of the economic evaluations are presented in Table 14.

Table 14: Key components of the economic evaluation

Component	Description
Type of analysis	Cost-utility analysis (base case)
Comparators	TEZ/IVA for F/F; TEZ/IVA for F/RF; and BSC for F/MF
Outcomes	Quality-adjusted life-years (base case)
Time horizon	Lifetime
Method used to generate results	Microsimulation
Cycle length	4-week cycle for first two years in the model, after that 52-week cycle applied
Discounting	5% for costs and benefits
Transition probabilities	Baseline patient characteristics: from Study 102, TRAFFIC, TRANSPORT, EVOLVE and EXPAND
	Baseline survival: the Irish CF database
	Baseline ppFEV ₁ decline: based on longitudinal registry analyses
	Refer to Table 15 for a summary of the sources for other transition probabilities applied to model
	Relationship of surrogate outcomes and survival: Liou 2001.
Costs of the proposed medicine (effective cost per pack)	\$ [REDACTED]/pack
Health utility	ppFEV ₁ level-based utility (expert opinion), post lung transplantation (Anyanwu 2002), treatment-specific utility increment (Study 102)
Software	Microsoft Excel using Visual Basic

Source: Developed during the evaluation based on Table 3.1.1, p176 of the submission

Abbreviations: BSC = best supportive care; CF = cystic fibrosis; 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; F/RF = CF patient heterozygous for the F508del in the CFTR gene with a residual function mutation; ITC = indirect comparison analysis; ppFEV₁ = percent predicted forced expiratory volume in one second; RCT = randomised controlled trial; TEZ/IVA = tezacaftor/ivacaftor

- 6.38 A summary of the data sources utilised in the economic evaluations is provided in Table 15. The ESC noted data inputs were applied interchangeably between populations without considering whether those data and their effects were exchangeable (e.g., treatment effect for pulmonary exacerbation for F/F and F/RF population were derived from the F/MF population). The pre-PBAC response stated the F/F and F/MF populations have a more severe disease phenotype and have similar disease trajectories and rates of lung function decline. The interchangeability of model inputs is therefore supported by the similarity in the disease trajectory (i.e. both severe phenotypes) and the fact that these data are derived from the same treatment (i.e. ELX/TEZ/IVA).

Table 15: Transition probabilities applied in economic models

Data input	F/F economic model		F/RF economic model		F/MF economic model
	ELX/ TEZ/ IVA	TEZ/IVA	ELX/ TEZ/ IVA	TEZ/IVA	ELX/TEZ/IVA
Absolute change in ppFEV ₁	ITC of Study 109 and EVOLVE	EVOLVE	ITC of Study 104 and EXPAND	EXPAND	Study 102
Absolute change in weight-for-age z-score (estimated from BMI outcome)	ITC of study 109 and EVOLVE	EVOLVE	ITC of study 104 and EXPAND	EXPAND	Study 102
Pulmonary exacerbations	Study 102	EVOLVE	Study 102	EXPAND, EXTEND	Study 102
Reduction in long-term decline in ppFEV ₁	Flume 2019, based on TEZ/IVA data (EXTEND and EVOLVE)	Konstan 2017, based on LUM/IVA data (TRAFFIC, TRANSPORT and PROGRESS)	Flume 2019 based on TEZ/IVA data (EXTEND and EVOLVE)	Konstan 2017 based on LUM/IVA data (TRAFFIC, TRANSPORT and PROGRESS)	Flume 2019 based on TEZ/IVA data (EXTEND and EVOLVE)

EVOLVE: TEZ/IVA study in F/F patients

EXPAND: TEZ/IVA study in F/RF patients

EXTEND: TEZ/IVA extension study in F/F and F/RF patients

TRAFFIC: LUM/IVA study in F/F patients

TRANSPORT: LUM/IVA study in F/F patients

PROGRESS: LUM/IVA extension study in FF/ patients

BSC = best supportive care; 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; F/RF = CF patient heterozygous for the F508del in the CFTR gene with a residual function mutation; ITC = indirect comparison analysis; ppFEV₁ = percent predicted forced expiratory volume in one second; TEZ/IVA = tezacaftor/ivacaftor

- 6.39 The baseline patient characteristics in the model differed from the Australian patients particularly in terms of lung function where only 2% of patients in the model had normal lung function compared with 28% of Australian patients (ACFDR 2019) (refer also paragraph 6.20). The largest difference was observed in the 12 to 18-year-old group where around half of patients in Australia have normal lung function compared to 4% in the model (see Table 10). The PSCR noted that if the model was modified to oversample patients with baseline ppFEV₁ > 90% so that over 28% of the patient cohort modelled had a ppFEV₁ > 90%, it had negligible impact on the ICER. The ESC considered this result may reflect that the analysis changed baseline ppFEV₁ levels only, without consideration of changes to other relevant parameters such as efficacy, and hence the analysis did not provide an accurate assessment of the cost-effectiveness of treating patients with better lung function at baseline. The ESC considered it is likely the incremental effectiveness of ELX/TEZ/IVA in patients with baseline ppFEV₁ > 90% would be lower resulting in a higher ICER compared with the ITT population. Thus the overall ICER is likely to be underestimated.
- 6.40 It was assumed in the models that the acute treatment effects on the surrogate outcome of ppFEV₁ (24 weeks for F/F and F/MF, 8 weeks for F/RF) had a lifetime impact on the final outcomes of PEx, lung transplantation, mortality and quality of

life. The PBAC previously considered that the difference in ppFEV₁ (between the active treatment and its relevant comparator), and hence the impact of treatment on final outcomes, may reduce over the long-term (paragraph 6.32, TEZ/IVA PSD, March 2019 PBAC meeting; RF).

- 6.41 The assumed decrease in rate of decline in ppFEV₁ throughout the model time horizon for TEZ/IVA was 42.0% of that for BSC for the F/F and F/RF populations. This resulted in divergence in ppFEV₁ for the TEZ/IVA and BSC arms over time which the ESC considered was not justified given the available data. The 42% decrease in the rate of decline was based on a study of LUM/IVA in F/F patients (Konstan 2017) (Table 16). The submission did not address whether there is any potential for differences across populations in the annual decline in ppFEV₁. The ESC noted data from LUM/IVA was assumed to be directly applicable to that for TEZ/IVA. The ESC recalled the PBAC considered a 42% rate of decline for LUM/IVA to be overly optimistic and that it may not be sustained in the long term (paragraph 7.7, LUM/IVA PSD, July 2018 PBAC meeting). The ESC recalled the cost effectiveness of LUM/IVA was highly sensitive to this assumption (Table 13, LUM/IVA PSD, July 2018 PBAC meeting).
- 6.42 The assumed decrease in rate of decline in ppFEV₁ throughout the time horizon of the model for ELX/TEZ/IVA was 61.5% of that for BSC for the F/F, F/RF and F/MF populations. This decrease in the rate of decline was based on a study of TEZ/IVA in F/F patients (Flume 2019) (Table 16). The submission did not address whether there is any potential for differences across populations in the annual rate of decline in ppFEV₁. Limited information was provided in the submission regarding the Flume 2019 study; however, a draft manuscript was provided with the PSCR. The ESC noted this study had not been evaluated. The ESC further noted data from TEZ/IVA was assumed to be directly applicable to that for ELX/TEZ/IVA and considered this assumption to be poorly supported and likely inappropriate. The ESC considered assuming this level of decline over the model time horizon to be overly optimistic and unlikely to be sustained in the long term, especially in the context of data for ELX/TEZ/IVA being currently available for no more than 48 weeks.
- 6.43 The PSCR stated available evidence for other CFTR modulators showed that the rate of ppFEV₁ decline is slowed compared to matched CFTR modulator-untreated controls and that this reduction is maintained over time. The PSCR stated the real-world evidence (provided as an attachment to the submission) shows that the modelled effect on the rate of decline of lung function for LUM/IVA and TEZ/IVA in previous PBAC submissions was conservative. The PSCR stated that given that ELX/TEZ/IVA was shown to be superior to TEZ/IVA in Study 103 and has demonstrated lung function improvements in clinical studies that are greater in magnitude than any other CFTR modulator studied to-date, it is reasonable to expect that ELX/TEZ/IVA will demonstrate reductions in the rate of lung function decline that are at least as large as those seen with TEZ/IVA.
- 6.44 The ESC noted the above assumptions resulted in a rate of decline in ppFEV₁ that was 19.5 percentage points slower in ELX/TEZ/IVA compared with TEZ/IVA (61.5% - 42.0%) for the F/F and F/RF populations, and 61.5 percentage points slower in

ELX/TEZ/IVA compared with BSC for the F/MF population. Applying a constant relative difference in ppFEV₁ over the model time horizon resulted in the absolute difference in ppFEV₁ diverging over time (see Figure 3). The ESC considered this divergence was unsupported in the context of the short follow-up data for treatment with ELX/TEZ/IVA, the rate of decline being based on data for different treatments, and based on a different population for the F/RF and F/MF populations. The pre-PBAC response stated the totality of evidence shows superiority of ELX/TEZ/IVA over current CFTR modulators with a further slowing in decline, and that, as with previous submissions, the sponsor is willing to work with the PBAC and the Department if substantiation of benefit is required, but this should not delay access of ELX/TEZ/IVA.

Table 16: Rate of decline of ppFEV₁ (relative to BSC; 0%)

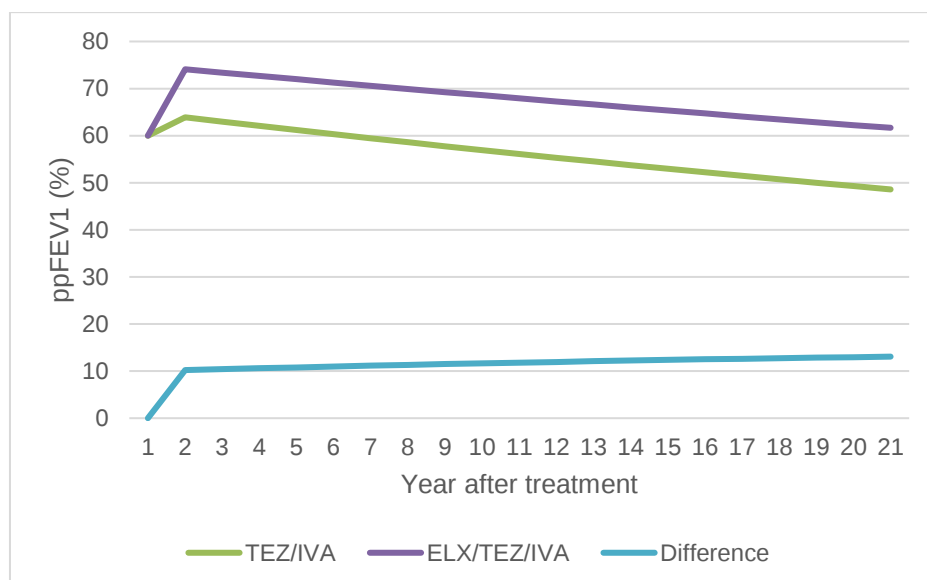
Comparison Study	Annual rate of ppFEV ₁ decline		Reduction rate	Source
	TEZ/IVA	BSC		
ELX/TEZ/IVA vs BSC Flume 2019	-0.80 (95% CI: -1.31, -0.30)	-2.08 (95% CI: -2.37, -1.82)	61.5%	This study reported data from a US registry-matched analysis of 407 F/F patients receiving TEZ/IVA (in EVOLVE and EXTEND) matched to 1,383 untreated F/F patients from the US CFFPR with mean duration of follow-up of two years.
	LUM/IVA	BSC		
TEZ/IVA vs BSC Konstan 2017	-1.33 (95% CI: -1.80, -0.85)	-2.29 (95% CI: -2.56, -2.03)	42.0%	TRAFFIC/TRANSPORT and PROGRESS, and US CFFPR. Comparing F/F patients receiving LUM/IVA versus match control i.e. BSC. Mean FU = 2 years.

Source: based on Table 3.1.17, p201 of the submission

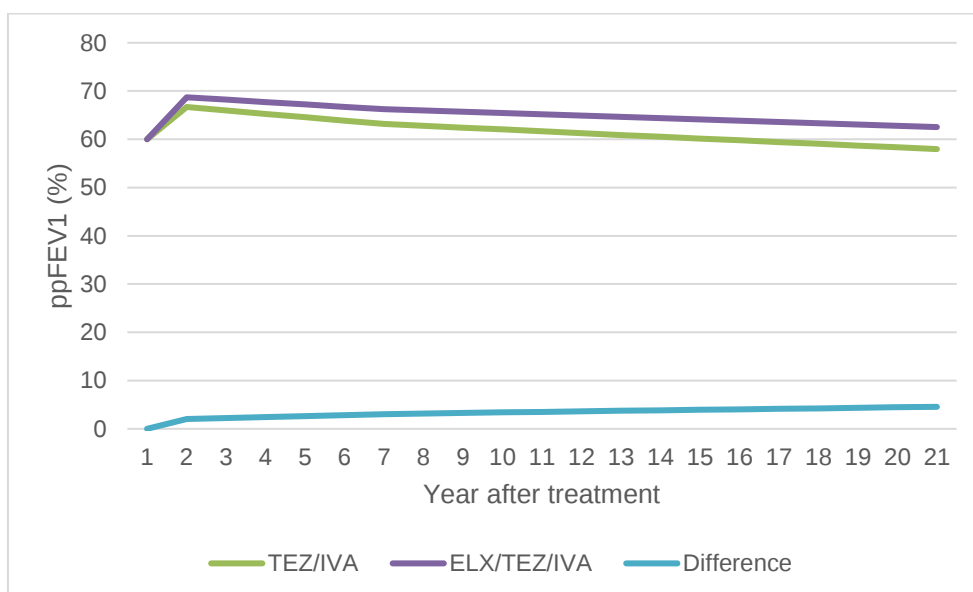
Abbreviations: BSC = best supportive care; CI = confidence interval; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; F/F, homozygous for F508del-CFTR mutations; ppFEV₁ = percent predicted forced expiratory volume in one second; FU = follow-up period; LUM/IVA = lumacaftor/ivacaftor; ppFEV₁, percent predicted forced expiratory volume in one second; TEZ/IVA = tezacaftor/ivacaftor

Figure 3: Rate of decline ppFEV1 for F/F (A), F/RF (B) and F/MF (C) populations from the economic model

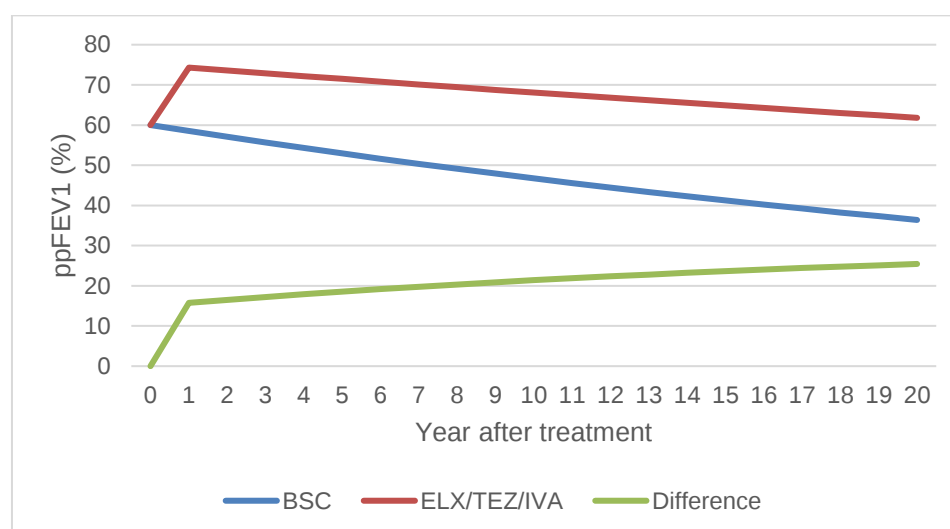
A. F/F population



B. F/RF population



C. F/MF population



Source: Developed during the evaluation based on data from Table 3.1.13, p199; Table 3.1.14, p199; Table 3.1.15, p200; Table 3.1.17, p201 of the submission

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

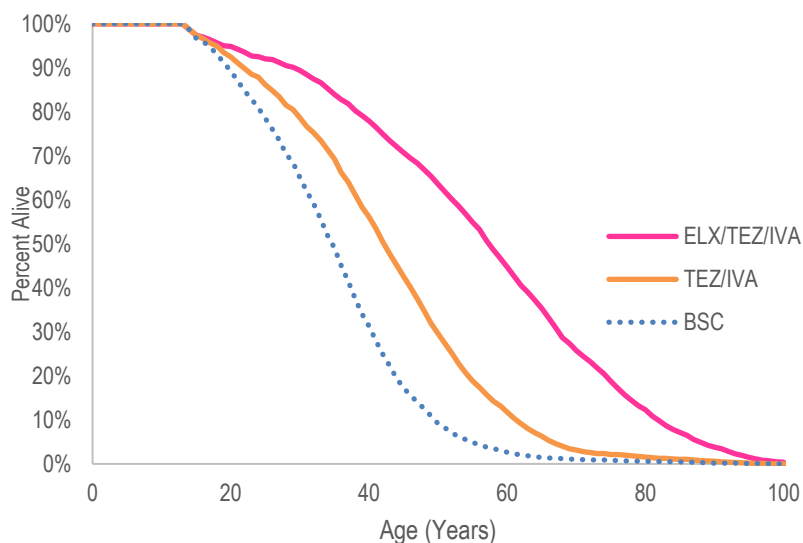
Note: Assumed that a patient aged 18 years with 60% ppFEV₁ at baseline

- 6.45 The PBAC noted the analyses provided to support the 42% and 61.5% decrease in rate of decline of ppFEV₁ combined data from study participants on therapy with historical control data from untreated CF patients in the United States Cystic Fibrosis Foundation Patient Registry (CFFPR). The PBAC recalled it had previously considered the use of the data from the CFFPR may not adequately support the claim of a reduction in rate of decline in ppFEV₁ (paragraph 6.26, LUM/IVA PSD, July 2018). The PBAC reiterated its concern that using patients in the CFFPR as a control arm may bias in favour of the CFTR modulators as treatment of these patients may not reflect best clinical practise.
- 6.46 The submission assumed compliance of 90% in the model and stated this was consistent with previous CFTR modulator submissions. This compliance rate was lower than in the trials which ranged between 98.8% and 100% (see Table 22 for details). The ESC considered this was inappropriate and that the use of compliance lower than in the trials (which results in a lower drug cost for the treatment and comparator arms) and assuming the same treatment effect as in the trials was not justified by the submission. The ESC considered this biased the analysis in favour of ELX/TEZ/IVA (higher absolute reduction for costs of ELX/TEZ/IVA as it has higher cost than its comparators) as it resulted in lower costs without affecting efficacy.
- 6.47 The submission maintained the use of utility values derived from CF experts (7 Australian CF centre directors) as previously seen by the PBAC (paragraph 6.45, LUM/IVA (age 12+), PSD, July 2018 PBAC meeting). The PBAC previously noted that the utility value applied for normal ppFEV₁ was higher than the general Australian population utility value. The ESC previously noted the utility weights used in the model were based on a small number of clinicians completing the EQ-5D-5L

questionnaire (paragraph 6.52, LUM/IVA PSD, July 2017 PBAC meeting). The ESC considered that the use of proxy completion in this way was likely to exaggerate differences between health states due to focusing effects, and hence reduce the ICER.

- 6.48 The submission applied a treatment-specific utility increment of 0.08 obtained from F/MF patients in Study 102 for those receiving ELX/TEZ/IVA and justified this to capture the benefits of ELX/TEZ/IVA that are not related to the impact on lung health (extrapulmonary). Application of the 0.08 increment resulted in the utility value of patients with normal lung function surpassing 1.00. In addition, the utility value of patients with mild lung function became 0.98, which is higher than the Australian norm (e.g. 0.91 based on McCaffrey et al 2016). The ESC considered applying a treatment specific increment in utility was inappropriate and biased the analysis in favour of ELX/TEZ/IVA. The pre-PBAC response defended the application of the utility increment as methodologically appropriate, evidence-based and consistent with the consumer feedback provided to the PBAC. However, to expedite access to ELX/TEZ/IVA and align with previous PBAC decision making, the pre-PBAC response accepted removal of the utility increment from the analysis. The pre-PBAC response reduced the requested effective price of ELX/TEZ/IVA from \$[REDACTED] to \$[REDACTED] per pack which resulted in the ICER for the base case as presented in the submission remaining at \$155,000 to < \$255,000/QALY.
- 6.49 The submission applied the time to loss of exclusivity (LoE) of [REDACTED] years for ELX/TEZ/IVA and [REDACTED] years for TEZ/IVA and assumed a price reduction due to generic entry into this market. The submission claimed that after LoE and the entry of generic products into this market, these medications will decrease in price compared to the original CFTR modulator's effective prices by 90%. Applying price decreases due to LoE was previously considered inappropriate by the PBAC (paragraph 6.52, LUM/IVA PSD, July 2018 PBAC meeting). This biased the analysis in favour of ELX/TEZ/IVA. The ESC reiterated the model should apply the proposed prices for the entire time horizon.
- 6.50 The traces of overall survival from the economic model for F/F, F/RF and F/MF population as presented in the submission are in Figure 4 to Figure 6.

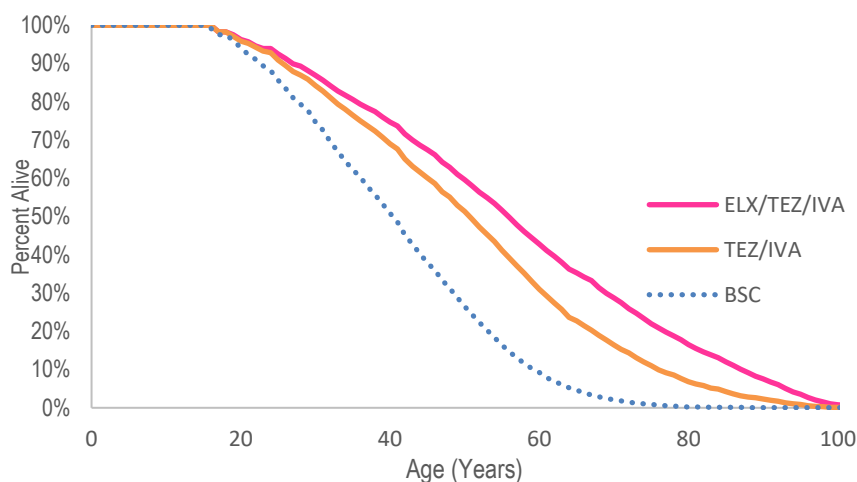
Figure 4: Overall survival predicted from the model between ELX/TEZ/IVA and TEZ/IVA and in F/F patients.



Source: Developed during the evaluation based on sheet 'results' of the economic model worksheet

Abbreviations: BSC = best supportive care; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; F/F = homozygous for F508del-CFTR mutations; TEZ/IVA = tezacaftor/ivacaftor

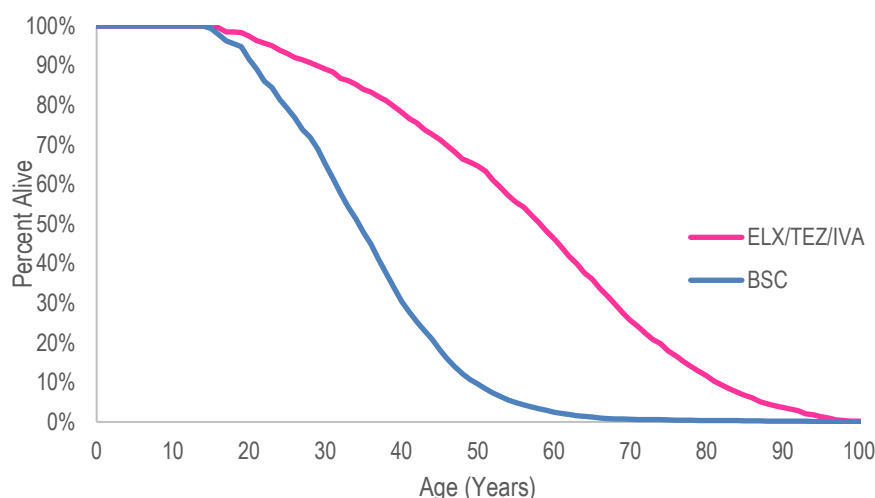
Figure 5: Overall survival predicted from the model between ELX/TEZ/IVA and TEZ/IVA in F/RF patients.



Source: Developed during the evaluation based on sheet 'results' of the economic model worksheet

Abbreviations: BSC = best supportive care; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; F/RF = heterozygous for F508del-CFTR with a second residual function mutation; TEZ/IVA = tezacaftor/ivacaftor

Figure 6: Overall survival predicted from the model between ELX/TEZ/IVA and BSC in F/MF patients.



Source: Developed during the evaluation based on sheet 'results' of the economic model worksheet

Abbreviations: BSC = best supportive care; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; F/MF = heterozygous for F508del-CFTR mutation with a second minimal function allele

6.51 The submission did not adequately validate the long-term survival of CF patients as presented within the economic model. It was also unclear how the submission derived different baseline survival curves for BSC across the relevant populations given that the Irish cohort reported the overall survival of CF patients (not by population).

6.52 A summary of the key drivers of the model is presented in the Table 17.

Table 17: Key drivers of the model

Description	Method/Value	Impact
LoE	Loss of exclusivity (LoE) of [REDACTED] years for ELX/TEZ/IVA and [REDACTED] years for TEZ/IVA, then prices of drug drop by 90%.	High, favours ELX/TEZ/IVA, removing LoE increased the ICERs
Time horizon	Lifetime in the base case analysis compared to 8 to 24 weeks in the clinical trials	High, favours ELX/TEZ/IVA; use of 20-year time horizon increased the ICERs
Long-term reduction in decline of ppFEV ₁	Long-term reduction in decline of ppFEV ₁ of 61.5% for ELX/TEZ/IVA, 42% of TEZ/IVA	High, favours ELX/TEZ/IVA; assuming the decline for ELX/TEZ/IVA is the same as TEZ/IVA (42%) increased the ICERs
Compliance	90% compliance rate applied in the model compared with those in the trials ranging between 98.8% to 100%	Moderate, favours ELX/TEZ/IVA, use of the compliance as in the trials increased the ICERs

Source: Developed during the evaluation

Abbreviations: 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; TEZ/IVA = tezacaftor/ivacaftor

6.53 The results of the economic evaluation are provided in Table 18.

6.54 The submission applied different annual costs of ELX/TEZ/IVA for each population (\$[REDACTED] for F/F, \$[REDACTED] for F/RF and \$[REDACTED] for F/MF) that resulted in an ICER

of \$155,000 to < \$255,000 per QALY gained across each subpopulation. These annual costs were then weighted according to the proportion of the subpopulation (57.5% for F/F, 5.9% for F/RF and 36.5% for F/MF²) and this resulted in the weighted price of ELX/TEZ/IVA of \$ [REDACTED]³ per year. The ESC considered use of the weighted annual price for each population in the economic model was informative as it enabled the relative value of ELX/TEZ/IVA in each population to be considered separately.

Table 18: Incremental cost-effectiveness estimates for the base case (based on ELX/TEZ/IVA pack price of \$ [REDACTED])

F/F	ELX/TEZ/IVA	TEZ/IVA	Incremental
Life Years	14.35	11.16	3.19
QALYs	11.88	7.33	4.55
Total Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
ICER (cost per LYG)			\$ [REDACTED] ¹
ICER (cost per QALY gained)			\$ [REDACTED] ²
F/RF	ELX/TEZ/IVA	TEZ/IVA	Incremental
Life Years	12.47	11.33	1.14
QALYs	10.64	8.40	2.25
Total Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
ICER (cost per LYG)			\$ [REDACTED] ³
ICER (cost per QALY gained)			\$ [REDACTED] ¹
F/MF	ELX/TEZ/IVA	BSC	Incremental
Life Years	14.23	8.79	5.44
QALYs	11.84	5.38	6.47
Total Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
ICER (cost per LYG)			\$ [REDACTED] ¹
ICER (cost per QALY gained)			\$ [REDACTED] ¹

Abbreviations: BSC = best supportive care; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; F/F = homozygous for F508del-CFTR mutations; F/MF = heterozygous for F508del-CFTR mutation with a second minimal function allele; F/RF = heterozygous for F508del-CFTR with a second residual function mutation; ICER= incremental cost effectiveness ratio; LYG = life years gained; QALYs= quality adjusted life years; TEZ/IVA = tezacaftor/ivacaftor

The redacted values correspond to the following ranges:

¹ \$155,000 to < \$255,000

² \$135,000 to < \$155,000

³ \$455,000 to < \$555,000

6.55 The submission conducted a cost analysis for the F/G population. Based on the proposed effective price (\$ [REDACTED] per 28-8 day pack, 11.74 packs per year), it was estimated that using ELX/TEZ/IVA compared with IVA (\$ [REDACTED] per 28-day pack) would result in a cost-saving of \$ [REDACTED] per patient per year⁴. The ESC noted the current RSA caps for IVA were based on an annual cost per patient of \$ [REDACTED], which

² Calculated as $F/F = 53.2 / (53.2 + 5.5 + 33.8)$, $F/RF = 5.5 / (53.2 + 5.5 + 33.8)$, F/MF and $F/\text{not yet characterised} = 33.8 / (53.2 + 5.5 + 33.8)$ using proportions from Table 26.

³ Calculated as $(365.25 / 28) \times \$ [REDACTED]$

⁴ The submission used a yearly cost of IVA of \$ [REDACTED] which was “calculated based on Year 1 cap in the Ivacaftor Deed of Agreement and the number of treated patients in the equivalent time period utilising Vertex data gathered in field”

takes into account the outcomes of the Pay for Performance arrangement which applied at time of listing.

- 6.56 The results of key univariate sensitivity analyses are summarised in Table 19 and Table 20. The results of sensitivity analyses suggest that the model was most sensitive to removing the LoE assumption, followed by setting the time horizon to 20 years and removing the treatment specific utility increment. The results were also sensitive to the assumptions on the long-term decline in ppFEV₁.

Table 19: Results of sensitivity analyses, ELX/TEZ/IVA vs TEZ/ IVA for F/F and F/RF population (based on ELX/TEZ/IVA pack price of \$ [REDACTED])

	F/F			F/RF		
	Incr cost	Incr QALY	ICER	Incr cost	Incr QALY	ICER
Base case	\$ [REDACTED]	4.55	\$ [REDACTED] ¹	\$ [REDACTED]	2.25	\$ [REDACTED] ²
LoE assumption removed (base case LoE)	\$ [REDACTED]	4.55	\$ [REDACTED] ²	\$ [REDACTED]	2.25	\$ [REDACTED] ³
LoE assumption of [REDACTED] for TEZ/IVA, consistent with LUM/IVA July 2018 submission (base case [REDACTED]). LoE assumption for ELX/TEZ/IVA removed (base case [REDACTED])	\$ [REDACTED]	4.55	\$ [REDACTED] ³	\$ [REDACTED]	2.25	\$ [REDACTED] ⁴
LoE assumption of 8/12/2026 for TEZ/IVA, consistent with LUM/IVA July 2018 submission (base case [REDACTED]).	\$ [REDACTED]	4.55	\$ [REDACTED] ²	\$ [REDACTED]	2.25	\$ [REDACTED] ³
20-year time horizon (base case lifetime years)	\$ [REDACTED]	3.02	\$ [REDACTED] ²	\$ [REDACTED]	1.46	\$ [REDACTED] ⁵
Treatment-specific utility increment removed (base case 0.08)	\$ [REDACTED]	3.41	\$ [REDACTED] ²	\$ [REDACTED]	1.26	\$ [REDACTED] ⁵
Compliance as in the trials ranging between 99.4%-100% (base case 90%)	\$ [REDACTED]	4.55	\$ [REDACTED] ²	\$ [REDACTED]	2.25	\$ [REDACTED] ³
Same reduction in long-term decline in ppFEV ₁ – 42% relative to BSC for both ELX/TEZ/IVA and TEZ/IVA (base case 61.5% vs 42%)	\$ [REDACTED]	3.32	\$ [REDACTED] ²	\$ [REDACTED]	1.64	\$ [REDACTED] ³
Zero reduction in long-term decline in ppFEV ₁ – 0% relative to BSC for both ELX/TEZ/IVA and TEZ/IVA (base case 61.5% vs 42%)	\$ [REDACTED]	2.72	\$ [REDACTED] ²	\$ [REDACTED]	1.51	\$ [REDACTED] ³

Source: Table 3.1.33 of the submission; developed during the evaluation based on the excel model

Abbreviations: BSC = best supporting care; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; F/F = homozygous for F508del-CFTR mutations; F/MF = heterozygous for F508del-CFTR mutation with a second minimal function allele; F/RF = heterozygous for F508del-CFTR with a second residual function mutation; ICER = incremental cost-effectiveness ratio; LoE = loss of exclusivity; PEx = pulmonary exacerbation; ppFEV₁ = percent predicted forced expiratory volume in one second; QALYs = quality-adjusted life-years; TEZ/IVA = tezacaftor/ivacaftor

The redacted values correspond to the following ranges:

¹ \$135,000 to < \$155,000

² \$155,000 to < \$255,000

³ \$255,000 to < \$355,000

⁴ \$455,000 to < \$555,000

⁵ \$355,000 to < \$455,000

Table 20: Results of sensitivity analyses, ELX/TEZ/IVA vs BSC, F/MF population (based on ELX/TEZ/IVA pack price of \$ [REDACTED])

	F/MF population		
	Incr cost	Incr QALY	ICER
Base case	\$ [REDACTED]	6.47	\$ [REDACTED] ¹
LoE assumption removed (base case LoE)	\$ [REDACTED]	6.47	\$ [REDACTED] ²
20-year time horizon (base case lifetime years)	\$ [REDACTED]	4.50	\$ [REDACTED] ¹
Treatment-specific utility increment removed (base case 0.08)	\$ [REDACTED]	5.36	\$ [REDACTED] ¹
Compliance as in the trial 98.4% (base case 90%)	\$ [REDACTED]	6.47	\$ [REDACTED] ¹
Reduction in long-term decline of 42% ppFEV ₁ relative to BSC for ELX/TEZ/IVA (base case 61.5%)	\$ [REDACTED]	5.29	\$ [REDACTED] ¹
Reduction in long-term decline of 0% ppFEV ₁ relative to BSC for ELX/TEZ/IVA (base case 61.5%)	\$ [REDACTED]	3.47	\$ [REDACTED] ²

BSC = best supporting care; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; F/MF = heterozygous for F508del-CFTR mutation with a second minimal function allele; LoE = loss of exclusivity; ppFEV₁ = percent predicted forced expiratory volume in one second; QALYs = quality-adjusted life-years; TEZ/IVA = tezacaftor/ivacaftor

The redacted values correspond to the following ranges:

¹ \$155,000 to < \$255,000

² \$255,000 to < \$355,000

6.57 The ESC proposed a multivariate analysis assuming (i) the same decrease in rate of decline for ELX/TEZ/IVA and TEZ/IVA (42%, base case used 61.5% for ELX/TEZ/IVA) (ii) removal of treatment specific utility benefit for ELX/TEZ/IVA (base case 0.08), (iii) the same price for ELX/TEZ/IVA and TEZ/IVA throughout the model time horizon (i.e. no reduction due to LoE) and (iv) compliance based on that observed in the trials. The ESC noted the ICER using the multivariate analysis for the F/F population (vs TEZ/IVA) was \$355,000 to < \$455,000 per QALY, for the F/RF population (vs TEZ/IVA) was \$955,000 to < \$1,055,000 per QALY and in the F/MF population (vs BSC) was \$355,000 to < \$455,000 per QALY.

Table 21: Revised ICERs specified by the ESC (based on ELX/TEZ/IVA pack price of \$ [REDACTED])

Patient Groups	F/F population, ELX/TEZ/IVA vs TEZ/IVA	F/RF population, ELX/TEZ/IVA vs TEZ/IVA	F/MF population, ELX/TEZ/IVA vs BSC
Base case ICER	\$ [REDACTED] ¹	\$ [REDACTED] ²	\$ [REDACTED] ²
Revised ICERs			
1. 42% rate of decline for ELX/TEZ/IVA (base case: 61.5%)	\$ [REDACTED] ³	\$ [REDACTED] ⁴	\$ [REDACTED] ³
2. Removal of treatment-related utility (base case 0.08)			
3. No LoE price reductions for ELX/TEZ/IVA or TEZ/IVA			
4. Compliance as per the clinical trials			

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

⁴ \$955,000 to < \$1,055,000

6.58 The ESC recalled the PBAC had previously considered the economic model for LUM/IVA should assume (paragraph 6.57, LUM/IVA PSD, July 2017 PBAC meeting):

- The estimated decline in ppFEV₁ in LUM/IVA treated patients set to 100% of BSC after 24 weeks.

- Assuming 75% of hospitalisations are due to PEx.
- Removal of the 5% statutory price reduction and the assumed 90% generic price reduction.

Under this scenario, the ICER for LUM/IVA would be approximately > \$1,055,000 and a cost per patient of \$ [REDACTED] per year was required to reduce the ICER to \$155,000 to < \$255,000/ QALY.

- 6.59 The ESC recalled that, in July 2018, the PBAC considered that while there was evidence that LUM/IVA slows the rate of decline in ppFEV₁ and reduces PEx up to 96 weeks for some patients; the sustainability of these benefits in the longer term remained uncertain. The PBAC recommended listing under a managed access program with PBS listing at \$ [REDACTED] per patient per year for a period of two and a half years to allow the sponsor to provide further data to satisfy the PBAC that the differences in the rates of decline in lung function (ppFEV₁) and pulmonary exacerbations observed over the 96 week trial period are sustained over a longer time period of at least 4 years in real clinical practice (paragraph 6.74, LUM/IVA PSD, July 2018 PBAC meeting). Should the PBAC not affirm cost-effectiveness of LUM/IVA at two and half years, the price paid should reduce to \$ [REDACTED] per patient per year. The ESC noted LUM/IVA was listed on the PBS on 1 October 2018 and thus the cost-effectiveness of LUM/IVA will need to be reconsidered in the first half of 2021.
- 6.60 The ESC considered the cost effective price of LUM/IVA and TEZ/IVA (as it was listed on the basis of cost-minimisation to LUM/IVA) remained uncertain.
- 6.61 The PBAC considered a cost-utility analysis for the F/RF population was not appropriate as the claim of superior effectiveness was not accepted. The PBAC considered a non-inferiority claim was reasonable and a cost-minimisation analysis (vs TEZ/IVA) was appropriate for this population.
- 6.62 For the F/F and F/MF populations, the PBAC considered it would be reasonable for the same model assumptions to apply that were accepted for LUM/IVA (and resulted in a cost of \$ [REDACTED] per patient per year). The following revisions to the submission's base case model were required (i) no treatment specific utility (ii) rate of decline in ppFEV₁ for ELX/TEZ/IVA of 42% and (iii) no increase in the cost of TEZ/IVA compared with that agreed previously for LUM/IVA. Using the weighted price provided in the pre-PBAC response (cost per patient per year \$ [REDACTED] assuming 90% compliance):
- For the F/F population, the resulting ICER was \$255,000 to < \$355,000 per QALY (vs TEZ/IVA). To achieve an ICER of \$155,000 to < \$255,000 per QALY, a cost per patient per year of \$ [REDACTED] (assuming 90% compliance) would be required. The PBAC noted that assuming a decrease in rate of decline of 61.5% for ELX/TEZ/IVA as proposed in the submission, resulted in an ICER of \$155,000 to < \$255,000 per QALY and a cost per patient per year of \$ [REDACTED] (assuming 90% compliance) would be required to achieve an ICER of \$155,000 to < \$255,000 per QALY.

- For the F/MF population, the resulting ICER was \$155,000 to < \$255,000 per QALY (vs BSC). To achieve an ICER of \$155,000 to < \$255,000 per QALY, a cost per patient per year of \$ [REDACTED] (assuming 90% compliance) would be required. The PBAC noted that assuming a decrease in rate of decline of 61.5% for ELX/TEZ/IVA as proposed in the submission, resulted in an ICER of \$155,000 to < \$255,000 per QALY and a cost per patient per year of \$ [REDACTED] (assuming 90% compliance) would be required to achieve an ICER of \$155,000 to < \$255,000 per QALY.

Drug cost/patient/year

- 6.63 The drug cost per patient per year ranged from \$ [REDACTED] to \$ [REDACTED] based on an effective price of \$ [REDACTED] per pack (see Table 22). This estimate was based on treatment interruption and compliance rates as in the trials. The drug cost per patient per year based on the economic model was lower due to lower compliance rates. The drug cost per patient per year based on the financial estimates was marginally different to the modelled estimates due to different treatment interruption rates.

Table 22: Drug cost per patient for proposed and comparator drugs

	ELX/TEZ/IVA			Comparator		
	Trial dose and duration	Model	Financial estimates	Trial dose and duration	Model	Financial estimates
F/F						
Cost/patient/ 28-day supply (A)	\$ [REDACTED]			TEZ/IVA: \$ [REDACTED] ^b		
Treatment interruption (B)	1.25%	2.50% ^a	1.10%	1.67%	14.30% ^a	1.10%
Compliance (C)	100%	90%	90%	100%	90%	90%
Cost/patient/ year (13.04 pack/year; D A*(1-B)*C*D)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
F/RF						
Cost/patient/ 28-day supply (A)	\$ [REDACTED]			TEZ/IVA: \$ [REDACTED] ^b		
Treatment interruption (B)	0%	4.9% ^a	0.8%	1.25%	8.1% ^a	0.8%
Compliance (C)	99.4%	90%	90%	99.7%	90%	90%
Cost/patient/ year (13.04 pack/year; D A*(1-B)*C*D)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
F/G						
Cost/patient/ 28-day supply (A)	\$ [REDACTED]			IVA: \$ [REDACTED]		
Treatment interruption (B)	0%	4.9% ^a	0.8%	1.25%	8.1% ^a	0.8%
Compliance (C)	99.4%	90%	90%	99.7%	90%	90%
Cost/patient/ year (13.04 pack/year; D A*(1-B)*C*D)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
F/MF						
Cost/patient/ 28-day supply (A)	\$ [REDACTED]			BSC: NA		
Treatment interruption (B)	1.67%	3.30% ^a	1.00%	NA	NA	NA
Compliance (C)	98.8%	90%	90%	NA	NA	NA
Cost/patient/ year (13.04 pack/year; D A*(1-B)*C*D)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	NA	NA	NA

Source: developed during the evaluation

Abbreviations: ELX = elxacaftor; F/F = homozygous for F508del-CFTR mutations; F/MF = heterozygous for F508del-CFTR mutation with a second minimal function allele; F/RF = heterozygous for F508del-CFTR with a second residual function mutation; IVA = ivacaftor; mg = milligram; NA = not applicable; TEZ = tezacaftor

Note: ^a applied only within trial period; ^b 11 pack/year maximum;

Estimated PBS usage & financial implications

6.64 This submission was not considered by the Drug Utilisation Sub Committee (DUSC). The submission used an epidemiological approach to estimate the financial impact of the proposed listing. A summary of the data sources and parameter values applied in the financial estimates is presented in Table 23.

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Table 23: Key inputs for financial estimates

Parameter	Source	Estimate				Comments
		F/F	F/RF	F/G	F/MF	
Eligible patients	ACFDR 2013–2017	2,182 patients				Number of CF patients over 12 years of age with at least one F508del, who have not received an organ transplant.
Number of net new patients	ACFDR	59/year				
Proportion of subpopulations	ACFDR data request	53.2%	5.5%	7.5%	33.8% (17.8% F/MF and 16% F/not yet)	The number of patients for F/MF likely overestimated as the submission included mutation-unidentified patients in F/MF. F/MF represents only 21% of known mutation in Australia.
Compliance rate for ELX/TEZ/IVA	Assumption	90%				Same as in the economic model.
Discontinuation rate (yearly) for ELX/TEZ/IVA	Study 109, Study 104, Study 102	1.1%	0.8%	0.8%	1.0%	Higher discontinuation rates were presented to the PBAC in previous CFTR submission (6.8% from TRAFFIC and TRANSPORT and 14.9% from PROGRESS; paragraph 6.68, LUM/IVA PSD, July 2018 PBAC meeting).
Proportion of patients expected to be treated with ELX/TEZ/IVA who will have reduced CTRF use.	Assumption	95%	90%	90%	NA	Used to determine offset.

Source: Developed during the evaluation based on Table 4.1.1, Table 4.2.5, Table 4.2.11, Table 4.2.7 of the submission.

Abbreviations: ACFDR = Australian Cystic Fibrosis Data Registry; AEMP = Approved ex-manufacturer price; CFTR = Cystic fibrosis transmembrane conductance regulator; ELX/TEZ/IVA = elxacaftor/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/RF = heterozygous for F508del-CFTR with a second residual function mutation; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Schedule of Pharmaceutical Benefits; TEZ/IVA = tezacaftor/ivacaftor

6.65 A summary of the estimated use and financial implications is presented in Table 24.

Table 24: Estimated use and financial implications (based on ELX/TEZ/IVA pack price of \$ [REDACTED])

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
TOTAL F/any population						
Estimated extent of use						
Number of patients treated	[REDACTED] ¹	[REDACTED] ¹	[REDACTED] ¹	[REDACTED] ¹	[REDACTED] ¹	[REDACTED] ¹
Number of scripts dispensed	[REDACTED] ²	[REDACTED] ²	[REDACTED] ²	[REDACTED] ²	[REDACTED] ²	[REDACTED] ²
Estimated financial implications of ELX/TEZ/IVA						
Cost to PBS less copayments	\$ [REDACTED] ³	\$ [REDACTED] ³	\$ [REDACTED] ³	\$ [REDACTED] ³	\$ [REDACTED] ³	\$ [REDACTED] ³
Estimated financial implications for TEZ/IVA, LUM/IVA, IVA						
Cost to PBS less copayments	-\$ [REDACTED] ⁴	-\$ [REDACTED] ⁴	-\$ [REDACTED] ⁴	-\$ [REDACTED] ⁴	-\$ [REDACTED] ⁴	-\$ [REDACTED] ⁴
Net financial implications						
Net cost to PBS	\$ [REDACTED] ⁴	\$ [REDACTED] ⁴	\$ [REDACTED] ⁴	\$ [REDACTED] ⁴	\$ [REDACTED] ⁴	\$ [REDACTED] ⁴
Net cost to MBS	\$ [REDACTED] ⁵	\$ [REDACTED] ⁵	\$ [REDACTED] ⁵	\$ [REDACTED] ⁵	\$ [REDACTED] ⁵	\$ [REDACTED] ⁵
Net cost to PBS/MBS	\$ [REDACTED] ⁴	\$ [REDACTED] ⁴	\$ [REDACTED] ⁴	\$ [REDACTED] ⁴	\$ [REDACTED] ⁴	\$ [REDACTED] ⁴

Source: Table 4.2.6, Table 4.4.2, Table 4.5.3 of the submission

Abbreviations: ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; TEZ/IVA = tezacaftor/ivacaftor

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 20,000 to < 30,000

³ \$200 million to < \$300 million

⁴ \$100 million to < \$200 million

⁵ \$0 to < \$10 million

6.66 The total cost to the PBS/RPBS of listing ELX/TEZ/IVA was estimated to be \$200 million to < \$300 million in Year 6, and a total of > \$1 billion in the first 6 years of listing. The net cost to the PBS using the effective price of the comparator was estimated at \$100 million to < \$200 million in Year 6, and a total of \$800 million to < \$900 million in the first 6 years of listing. The pre-PBAC response stated the net cost to the PBS using the revised effective price was \$600 million to < \$700 million in the first 6 years of listing.

6.67 The submission estimated the number of F/F, F/RF and F/G treated patients i.e., the currently PBS-subsidised population, at 500 to < 5,000 (Table 25). The submission's estimate of the treated F/G patients appeared to be close to the PBS utilisation data provided by the DUSC Secretariat. However, the estimate for the F/F and F/RF patients was about 40% higher than the currently CFTR-treated patients (TEZ/IVA and LUM/IVA) suggested by the utilisation data as approximately 500 to < 5,000 patients. The PSCR stated the sponsor is open to discussions regarding a Risk Share

Arrangement for ELX/TEZ/IVA, TEZ/IVA, LUM/IVA and IVA that mitigates the uncertainty surrounding the utilisation and financial impact of all CFTR modulators.

Table 25: Comparison of the number of treated patients for the F/F, F/RF and F/G populations

	Estimated number of patients treated with ELX/TEZ/IVA in Year 1	Estimated number of treated patients based on PBS utilisation data
F/F and F/RF population	F/F: ■ ¹ F/RF: ■ ² Total: ■ ¹	■ ¹ patients treated with LUM/IVA (as of November 2020) (which includes patients 2 years and older). Estimated ■ ² patients > 12 years of age. ■ ² patients treated with TEZ/IVA (as of October 2020). Total: ■ ¹ treated patients.
F/G population	■ ²	■ ² patients treated with IVA (as of Q4 2020) (which includes patients aged 12 months old and older).

Abbreviations: 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/RF = heterozygous for F508del-CFTR with a second residual function mutation; LUM/IVA=lumacaftor/ivacaftor; IVA=ivacaftor; PBS = Pharmaceutical Benefits Scheme; TEZ/IVA = tezacaftor/ivacaftor

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² < 500

6.68 The distribution of the different F508del mutations was obtained from the ACFDR (Table 26). The submission assumed patients classified as F/not yet characterised should be added to the F/MF population. This resulted in the F/MF population accounting for 33.8% of the total population. The ESC noted the approach used in the submission may have overestimated the proportion of F/MF patients which resulted in underestimating the proportion of use accounted for by other populations which would underestimate the offsets for TEZ/IVA, LUM/IVA and IVA. The PSQR acknowledged that as genotyping of the second allele increases, together with characterisation of these mutations, patients will eventually be characterised as either F/G, F/RF or F/MF genotype. To determine the proportion of each phenotype within the F/any population, the PBAC considered it was reasonable to consider that 50% of the 354 patients in the ACFDR registry assumed by the submission to be in the F/not yet characterised population would be subsequently characterised to the F/MF population, 25% to the F/ G population and 25% to the F/RF population. Based on this allocation, the PBAC considered that within the F/any population 53.2% would be F/F, 9.5% would be F/RF, 25.8% would be F/MF and 11.5% would be F/G. For the purpose of calculating a weighted price (as described in paragraph 6.54), this reallocation would result in the F/F population accounting for 60.1% of the cost per patient per year, the F/RF population accounting for 10.7% and F/MF population accounting for 29.1%⁵.

⁵ Does not add to 100% due to rounding

Table 26: Proportion of patients within each population

Population (over 12 years of age)	Approach used in submission (assumed F/not yet should be added to the F/MF population)		Approach considered reasonable by the PBAC	
	Number of patients in ACFDR analysis	%	Number of patients in ACFDR analysis	%
F/F	1,180	53.2	1,180	53.2
F/RF	122	5.5	211	9.5
F/G	166	7.5	255	11.5
F/MF	395	17.8	572	25.8
F/not yet	354 ¹	16.0		
Total	2,217		2,217	

Abbreviations: ACFDR=Australian Cystic Fibrosis Data Registry; F/F = homozygous for F508del-CFTR mutations; F/MF = heterozygous for F508del-CFTR mutation with a second minimal function allele; F/RF = heterozygous for F508del-CFTR with a second residual function mutation; F/not yet= heterozygous for F508del-CFTR mutation that is unknown or not yet characterised; PBAC= Pharmaceutical Benefits Advisory Committee.

Calculated as 2,217-1,180-122-166-395

- 6.69 The submission stated that there are < 500 patients receiving ELX/TEZ/IVA via an early access program run by the sponsor for which grandfathering onto the PBS will be required. The PBAC noted that grandfathered patients would be captured in the revised patient numbers referred to in paragraph 6.74
- 6.70 Overall, the net financial impact in the submission was overestimated mainly due to the overestimated number of treated patients and the underestimated cost-offset.
- 6.71 The PBAC considered it would be reasonable to use the number of F/F, F/RF and F/G patients accounted for at the time of listing of TEZ/IVA, LUM/IVA and IVA and agreed by the sponsor for the purposes of the current RSAs for those products, in order to calculate the incremental cost of listing ELX/TEZ/IVA for the F/any population. The PBAC noted the number of F/MF treated patients could be estimated based on the patient split outlined in paragraph 6.68.

Table 27: Estimated number of patients that would be eligible for treatment with ELX/TEZ/IVA.

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of F/F and F/RF patients over 12 years of age based on TEZ/IVA and LUM/IVA RSA	■ ³	■ ³	■ ³	■ ³	■ ³
Number of F/F patients (~85%)	■ ³	■ ³	■ ³	■ ³	■ ³
Number of F/RF patients (~15%)	■ ⁴	■ ⁴	■ ⁴	■ ⁴	■ ⁴
Number of F/G patients based on IVA RSA	■ ⁴	■ ⁴	■ ⁴	■ ⁴	■ ⁴
Number of F/G patients over 12 years of age ¹	■ ⁴	■ ⁴	■ ⁴	■ ⁴	■ ⁴
Number of F/MF patients over 12 years of age ²	■ ⁴	■ ⁴	■ ⁴	■ ⁴	■ ⁴

Abbreviations: ELX/TEZ/IVA = ellexacaftor/tezacaftor/ivacaftor; F/any = at least one F508del-CFTR mutation; F/F = homozygous for F508del-CFTR mutations; F/MF = heterozygous for F508del-CFTR mutation with a second minimal function allele; F/RF = heterozygous for F508del-CFTR with a second residual function mutation; LUM/IVA=lumacaftor/ivacaftor; IVA=ivacaftor; TEZ/IVA = tezacaftor/ivacaftor; RSA =risk sharing arrangement

1. Assuming 71% of CF patents over 12 months of age are over 12 years of age (calculated based on data in the ACFRD publication)

2. Assuming the F/MF population accounts for 25.8% of the F/any population (see paragraph 6.68)

The redacted values correspond to the following ranges:

³ 500 to < 5,000

⁴ < 500

- 6.72 The PBAC noted utilisation in the F/F, F/RF and F/G populations has been less than the expected patient numbers at time of listing and for the purposes of the RSAs for LUM/IVA, TEZ/IVA and IVA and therefore the PBAC considered a revision to the patient numbers to account for the listing of ELX/TEZ/IVA for these populations was not justified. For example, for the 12 months from December 2019, the previously agreed patient estimates covered a total of 500 to < 5,000 patients (across all populations and age groups); however, approximately 500 to < 5,000 patients were treated (calculated based on script numbers). The PBAC noted the F/MF population is not covered by any existing listing.
- 6.73 The PBAC considered it was reasonable to assume uptake of ELX/TEZ/IVA in the eligible F/F population would be 75% in Year 1, increasing to 85% in Year 5; in the eligible F/MF population would be 75% in Year 1, increasing to 100% in Year 5 and in the eligible F/G and F/RF population would be 50% per year. The PBAC considered it was appropriate to assume 100% uptake in the F/MF population in Year 5 as the number of patients was based on a treated population and, unlike the F/F, F/G and F/RF populations, the F/MF population have no other treatment options.
- 6.74 The PBAC considered the number of patients electing treatment with ELX/TEZ/IVA as summarised in Table 28 provided a reasonable basis to determine the net financial impact of the proposed listing and subsequent changes to existing RSAs.

Table 28: Estimated number of patients electing treatment with ELX/ TEZ/ IVA

	Year 1	Year 2	Year 3	Year 4	Year 5
F/F population					
Number of patients eligible for ELX/TEZ/IVA	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
% electing treatment with ELX/TEZ/IVA	75%	80%	85%	85%	85%
Number of patients electing treatment with ELX/TEZ/IVA	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
F/RF population					
Number of patients eligible for ELX/TEZ/IVA	■ ²	■ ²	■ ²	■ ²	■ ²
% electing treatment with ELX/TEZ/IVA	50%	50%	50%	50%	50%
Number of patients electing treatment with ELX/TEZ/IVA	■ ²	■ ²	■ ²	■ ²	■ ²
F/G population					
Number of patients eligible for ELX/TEZ/IVA	■ ²	■ ²	■ ²	■ ²	■ ²
% electing treatment with ELX/TEZ/IVA	50%	50%	50%	50%	50%
Number of patients electing treatment with ELX/TEZ/IVA	■ ²	■ ²	■ ²	■ ²	■ ²
F/MF population					
Number of patients eligible for ELX/TEZ/IVA	■ ²	■ ²	■ ²	■ ²	■ ²
% electing treatment with ELX/TEZ/IVA	75%	85%	95%	100%	100%
Number of patients electing treatment with ELX/TEZ/IVA	■ ²	■ ²	■ ²	■ ²	■ ²

Abbreviations: ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; F/any = at least one F508del-CFTR mutation; F/F = homozygous for F508del-CFTR mutations; F/MF = heterozygous for F508del-CFTR mutation with a second minimal function allele; F/RF = heterozygous for F508del-CFTR with a second residual function mutation; LUM/IVA=lumacaftor/ivacaftor; IVA=ivacaftor; TEZ/IVA = tezacaftor/ivacaftor; RSA =risk sharing arrangement

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² < 500

Quality Use of Medicines

- 6.75 The submission provided a list of activities proposed by the sponsor to support the quality use of medicines (QUM) on listing of ELX/TEZ/IVA. These activities appear to

be focused on patient support programs, including ‘holistic care packages’ and health care provider education. The submission has not outlined the specific QUM issues associated with the prescription and use of ELX/TEZ/IVA that activities outlined are designed to address.

Financial Management – Risk Sharing Arrangements

- 6.76 The submission stated the sponsor is open to discussions regarding a Risk Sharing Arrangement to mitigate uncertainty surrounding the utilisation and financial impact of listing ELX/TEZ/IVA but did not provide any detail in the submission.
- 6.77 During its consideration of LUM/IVA for F/F patients in July 2018 the PBAC was concerned that the assumptions regarding the rate of decline in lung function was overly optimistic and the rate of decline difference might not be sustained in the longer term (paragraph 7.7, LUM/IVA PSD, July 2018 PBAC meeting). The PBAC considered LUM/IVA would be acceptably cost-effective at a cost of \$ [REDACTED] per patient per year for a period of two and a half years. This allows the sponsor to provide further data to satisfy the PBAC that the differences in the rate of decline in lung function and pulmonary exacerbations observed over the 96 week trial period are sustained over a longer time period of at least 4 years in clinical practice (paragraph 6.74, LUM/IVA PSD, July 2018 PBAC meeting).
- 6.78 During its consideration of TEZ/ IVA for F/F patients in March 2019, the PBAC noted the effectiveness of TEZ/IVA was even more uncertain than that for LUM/IVA. The PBAC advised the same managed access requirements that applied to LUM/IVA should also apply to TEZ/IVA to manage risks around the uncertain effectiveness and whether the treatment benefit in terms of the decrease in rate of decline in lung function would be sustained in the longer term (paragraph 7.9, TEZ/IVA PSD, March 2019 PBAC meeting).
- 6.79 Given there are similar uncertainties associated with ELX/TEZ/IVA the PBAC considered it was appropriate for similar managed access requirements that apply to TEZ/IVA and LUM/IVA apply to ELX/TEZ/IVA. Further, the PBAC considered it was appropriate for any revisions to the circumstances associated with the listing of TEZ/IVA be flowed on to ELX/TEZ/IVA. The pre-PBAC response stated that, as with previous submissions, the sponsor is willing to work with the PBAC and the Department if substantiation of benefit is required, but further noted this should not delay access of ELX/TEZ/IVA.

7 PBAC outcome

- 7.1 The PBAC deferred making a recommendation to list elxacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) for the treatment of cystic fibrosis (CF) patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The PBAC considered ELX/TEZ/IVA provided a significant benefit for some patients, in particular, the F/F and F/MF populations. The PBAC considered the safety and effectiveness of ELX/TEZ/IVA beyond 48 weeks was uncertain but this could be managed with an appropriate Managed Access Program (MAP) similar to what is in place for the other CFTR modulators. The PBAC deferred making a recommendation in order to allow engagement with the sponsor to align the proposed listing of ELX/TEZ/IVA, and associated costs and financial implications with the MAP and risk share arrangements (RSA) of the currently listed CFTR modulators, with the cost-effectiveness link with these comparators having not satisfactorily been established by the submission.
- 7.2 The PBAC noted the submission presented evidence for four distinct populations with at least one F508del mutation in the CFTR gene: F/F, F/RF, F/MF and F/G. The PBAC considered the clinical evidence, cost-effectiveness and financial impact separately for the four populations making up the F/any population. The PBAC noted the submission included a fifth population, the F/not yet characterised population, and the submission assumed the efficacy, safety and cost-effectiveness of ELX/TEZ/IVA in the F/MF population was representative of that in the F/not yet characterised population. The PBAC assessed that the F/not yet characterised population should not be considered as a distinct patient population but rather the underlying phenotype of these patients would be F/MF, F/RF or F/G and therefore their cost effectiveness should be considered accordingly. The PBAC considered it would be reasonable to assume that 50% of patients included in the F/not yet characterised population in the submission are allocated to the F/MF population, 25% to the F/RF population and 25% to the F/G population.

Patients who are homozygous for the F508del-CFTR mutation (F/F population).

- 7.3 The PBAC considered the nominated main comparator of TEZ/IVA was reasonable in this population.
- 7.4 The PBAC was satisfied that ELX/TEZ/IVA provides, for some patients, an improvement in efficacy over TEZ/IVA, however the PBAC noted the uncertainty around long term outcomes.
- 7.5 The PBAC considered that treatment with ELX/TEZ/IVA provided a significant improvement in outcomes of ppFEV₁, CFQ-R Respiratory Domain score and sweat chloride up to 24 weeks versus TEZ/IVA (based on Study 109). The PBAC noted the improvement in ppFEV₁ was greater than the MCID of 10% at 24 weeks (10.2%). The PBAC noted there was limited evidence presented for the BMI outcome and evidence for the PEx outcome was limited to adverse event reporting. The PBAC noted no

comparative evidence was presented for ELX/TEZ/IVA versus TEZ/IVA beyond 24 weeks. The PBAC noted no evidence was provided for ELX/TEZ/IVA regarding the rate of decline in ppFEV₁ beyond 48 weeks.

- 7.6 The PBAC considered the claim of non-inferior safety compared to TEZ/IVA was adequately supported for up to 24 weeks. The PBAC noted no data beyond 24 weeks was available for Study 109 but an additional 36 weeks of non-comparative safety data was available for Study 103 (a 4 week study).
- 7.7 The PBAC noted no evidence was provided in patients with normal lung function (i.e., ppFEV₁>90%) and it was unknown if treatment with ELX/TEZ/IVA resulted in improved outcomes compared with TEZ/IVA in patients with normal lung function. The PBAC considered exclusion of patients with normal lung function from the clinical trials was likely to overestimate the overall comparative treatment benefit for ELX/TEZ/IVA. The PBAC noted that approximately 28% of all Australian CF patients and 52% of CF patients aged between 12 and 17 years have normal lung function. Additionally, there was no data presented to support the comparative benefit in patients with ppFEV₁<40.
- 7.8 The PBAC noted a modelled economic evaluation was presented for the F/F population comparing TEZ/IVA with BSC and then ELX/TEZ/IVA with TEZ/IVA, and that the structure of the model was similar to that considered for previous CFTR modulator therapies.
- 7.9 The PBAC considered the base case model presented in the submission should be revised to apply the same model assumptions that were accepted for LUM/IVA (and resulted in a cost of \$[REDACTED] per patient per year) to ELX/TEZ/IVA (as outlined in paragraph 6.62, provided ELX/TEZ/IVA is subject to the same MAP criteria as the current dual CFTR modulators and shares the same RSA).
- 7.10 The PBAC considered the cost-effectiveness of ELX/TEZ/IVA would be acceptable at an ICER of \$155,000 to < \$255,000 per QALY and noted that it would be satisfied that this ICER is being met where:
- The annual cost per patient requested by the sponsor in its pre-PBAC response of \$[REDACTED] is implemented for the supply of ELX/TEZ/IVA for the F/F population for the first 24 weeks of PBS listing only, noting that within this timeframe in Study 109 the improvement in ppFEV₁ was clinically significant and no decline in ppFEV₁ was observed; and
 - An annual cost per patient of \$[REDACTED] is implemented for the supply of ELX/TEZ/IVA for the F/F population for a further 2 years of listing allowing for a decrease in rate of decline in ppFEV₁ of 61.5% (paragraph 6.62); and
 - An annual cost per patient of \$[REDACTED] is implemented for the supply of ELX/TEZ/IVA for the F/F population for any supply beyond 2.5 years post listing on the PBS assuming a decrease in rate of decline of ppFEV₁ of 42% (paragraph 6.62).

- 7.11 The PBAC noted a key uncertainty with the economic model is the rate of decline in ppFEV₁ over the long term with ELX/TEZ/IVA and considered the uncertainty associated with the use of a 61.5% and a 42% rate of decline in ppFEV₁ could be addressed by provision of additional data, similar to what is currently in place for the MAP for the dual CFTR modulator therapies (LUM/IVA and TEZ/IVA).
- 7.12 The PBAC noted the current RSA for TEZ/IVA is designed to achieve a maximum cost per patient per year of \$ [REDACTED] but this is subject to the outcome of the MAP for LUM/IVA and TEZ/IVA and may reduce to as low as \$ [REDACTED]. The PBAC considered it is appropriate for any reduction in the cost per patient per year of TEZ/IVA as a result of the MAP should flow to ELX/TEZ/IVA such that there is no increase in the ICER.
- 7.13 The PBAC considered the RSA in place for LUM/IVA and TEZ/IVA adequately accounts for the eligible patient population and no increase in patient numbers would be justified for the F/F population. The PBAC noted that the expenditure caps in place for LUM/IVA and TEZ/IVA would need to increase to account for any additional cost per patient per year for patients treated with ELX/TEZ/IVA.

Patients who are heterozygous for F508del in the CFTR gene with a residual function mutation (F/RF population).

- 7.14 The PBAC considered the nominated main comparator of TEZ/IVA was reasonable in this population.
- 7.15 The PBAC noted the evidence presented for outcomes of ppFEV₁, CFQ-R Respiratory Domain score and sweat chloride were based on a short duration of treatment (8 weeks). The PBAC noted the improvement in ppFEV₁ (2.0%) was less than the 10% MCID, and that there was no evidence presented for BMI and evidence for the PEx outcome was limited to adverse event reporting. The PBAC considered the claim of superior effectiveness compared to TEZ/IVA was not adequately supported but a claim of non-inferiority was reasonable.
- 7.16 The PBAC considered the claim of non-inferior safety compared to TEZ/IVA was adequately supported for up to 8 weeks and further supported by the comparative data to 24 weeks provided for the F/F population.
- 7.17 The PBAC considered ELX/TEZ/IVA would be of acceptable cost-effectiveness if it was cost-minimised to TEZ/IVA for the F/RF population. The PBAC considered that, based on the data presented, it could not determine that ELX/TEZ/IVA provided any improved efficacy or safety over the comparator TEZ/IVA for the F/RF population. The PBAC noted that any reduction to the TEZ/IVA price, including through the outcome of the MAP, should be flowed on to ELX/TEZ/IVA.
- 7.18 The PBAC considered the equi-effective doses were elexacaftor 200 mg once daily/ tezacaftor 100 mg once daily/ ivacaftor 150 mg every 12 hours and tezacaftor 100 mg once daily/ ivacaftor 150 mg every 12 hours.
- 7.19 The PBAC considered the current RSA arrangement in place for LUM/IVA and TEZ/IVA adequately accounts for the eligible patient population and no increase in patient

numbers would be justified for the F/RF population. The PBAC noted that the expenditure caps in place for LUM/IVA and TEZ/IVA would need to increase to account for the additional cost per patient per year for patients treated with ELX/TEZ/IVA, driven by the weighted average price across the F/any population.

Patients who are heterozygous for F508del in the CFTR gene with a minimal function mutation (F/MF population).

- 7.20 The PBAC considered the nominated main comparator of BSC was reasonable in this population.
- 7.21 The PBAC was satisfied that ELX/TEZ/IVA provides, for some patients, a significant improvement in efficacy over BSC.
- 7.22 The PBAC considered the evidence presented indicated a significant improvement in all key outcomes including ppFEV₁, CFQ-R Respiratory Domain score, sweat chloride, BMI, and PEx at 24 weeks versus BSC. The PBAC noted the improvement in ppFEV₁ was greater than the MCID of 10% at 24 weeks (14.3%).
- 7.23 The PBAC considered the claim of non-inferior safety compared to BSC was adequately supported for up to 24 weeks. The PBAC noted an additional 24 weeks of non-comparative safety data was available.
- 7.24 The PBAC noted a modelled economic evaluation was presented for the F/MF population comparing ELX/TEZ/IVA with BSC, and that the structure of the model was similar to that considered by the PBAC for previous CFTR directed therapies.
- 7.25 The PBAC considered the base case model presented in the submission should be revised to include the same model assumptions that were accepted for LUM/IVA (as outlined in paragraph 6.62), provided ELX/TEZ/IVA is subject to similar MAP criteria and RSA.
- 7.26 The PBAC considered the cost-effectiveness of ELX/TEZ/IVA would be acceptable at an ICER of \$155,000 to < \$255,000 per QALY and noted that it would be satisfied that this ICER is being met where:
- The annual cost per patient requested by the sponsor in its pre-PBAC response of \$ [REDACTED] is implemented for the supply of ELX/TEZ/IVA for the F/MF population for the first 24 weeks of PBS listing only, noting that within this timeframe the improvement in ppFEV₁ was clinically significant and no decline in ppFEV₁ was observed; and
 - An annual cost per patient of \$ [REDACTED] is implemented for the supply of ELX/TEZ/IVA for the F/MF population for a further 2 years of listing, assuming a decrease in rate of decline in ppFEV₁ of 61.5% (paragraph 6.62); and
 - An annual cost per patient of \$ [REDACTED] is implemented for the supply of ELX/TEZ/IVA for the F/MF population for any supply beyond 2.5 years post listing on the PBS, assuming a decrease in rate of decline in ppFEV₁ of 42% (paragraph 6.62).

- 7.27 The PBAC noted a key uncertainty with the economic model is the rate of decline in ppFEV₁ over the long term with ELX/TEZ/IVA, and considered the uncertainty associated with the use of a 61.5% and a 42% rate of decline in ppFEV₁ could be addressed by provision of additional data through a MAP, similar to what is currently in place for the dual CFTR modulator therapies (LUM/IVA and TEZ/IVA).
- 7.28 The PBAC noted that the expenditure caps in place for LUM/IVA and TEZ/IVA would need to increase to account for the cost of treating this additional, currently untreated patient population. The PBAC considered the number of F/MF patients likely to be treated with ELX/TEZ/IVA presented in paragraph 6.74 and Table 28 was reasonable.

Patients who are heterozygous for F508del in the CFTR gene with a gating mutation (F/G population).

- 7.29 The PBAC considered the nominated main comparator of IVA was reasonable in this population.
- 7.30 The PBAC noted the evidence presented for outcomes of ppFEV₁, CFQ-R Respiratory Domain score and sweat chloride were based on a short duration of treatment (8 weeks). The PBAC noted the improvement in ppFEV₁ (5.8%) was less than the 10% MCID and that there was no evidence presented for BMI and evidence for the PEx outcome was limited to adverse event reporting. The PBAC considered the claim of superior effectiveness compared to IVA was not adequately supported but a claim of non-inferiority was reasonable.
- 7.31 The PBAC considered that, consistent with the methodology proposed in the submission, it was reasonable for the cost of ELX/TEZ/IVA for the F/G population to be calculated as the weighted average price of that for the F/F, F/RF and F/MF populations (see paragraph 7.33). The submission stated that treatment with ELX/TEZ/IVA would be cost-saving compared to treatment with IVA and the PBAC considered ELX/TEZ/IVA would be cost-effective for this population at the weighted price if the savings are realised in practice. The PBAC considered the current expenditure caps in place for IVA would need to reduce proportionately in order to realise these savings in practice. The PBAC noted the expenditure caps in place for LUM/IVA and TEZ/IVA would need to increase as F/G patients are not currently accounted for.

Weighted price calculation for ELX/TEZ/IVA.

- 7.32 The PBAC considered it was reasonable to calculate the weighted price for ELX/TEZ/IVA based on a split of F/F:F/RF:F/MF of 60.1:10.7:29.1 (paragraph 6.68).
- 7.33 The PBAC noted that based on this split that the following weighted costs can be calculated for ELX/TEZ/IVA to remain cost effective:
- The annual cost per patient of \$ [REDACTED] is implemented for the supply of ELX/TEZ/IVA for the F/any population for the first 24 weeks of PBS listing only; and

- The annual cost per patient of \$ [REDACTED] implemented for the supply of ELX/TEZ/IVA for the F/any population for a further 2 years of listing; and
- That the annual cost per patient of \$ [REDACTED] is implemented for the supply of ELX/TEZ/IVA for the F/any population for any supply beyond 2.5 years post listing on the PBS.

7.34 The PBAC noted that the MAP in place for the dual CFTR modulator therapies (LUM/IVA and TEZ/IVA) is due to conclude, with outcomes of that MAP to be submitted to the PBAC for consideration at its July 2021 meeting. In the context of further data being made available that may provide a higher level of certainty around the long term cost effectiveness and longer term health outcomes of these therapies, in particular the decrease in rate of decline of ppFEV₁, the PBAC considered that it would likely be in a position to provide updated advice to the Minister at that time. Such advice would likely cover the cost effectiveness of the broader group of CFTR modulator therapies, as well as ELX/TEZ/IVA more specifically, taking into account the latest available evidence. The PBAC therefore considered that should the sponsor wish to provide a submission based on the current advice for listing of ELX/TEZ/IVA on the PBS, it would need to do so at least six weeks prior to the July 2021 PBAC meeting.

Financial implications of listing for the F/any population

- 7.35 The PBAC considered the epidemiology approach to estimating the number of patients likely to be treated with ELX/TEZ/IVA resulted in a substantial overestimate of patient numbers and did not provide a reliable basis to estimate the financial implications of listing ELX/TEZ/IVA. The PBAC noted patient numbers have been previously agreed to for the F/F and the F/RF populations (at the time of listing TEZ/IVA + LUM/IVA) and the F/G population (for the purposes of the current IVA RSA). The PBAC noted the current use is less than the agreed patient numbers and considered there was no justification for an increase in patient numbers for the F/F, F/R and F/G populations.
- 7.36 The PBAC considered it was reasonable to estimate the number of patients expected to be treated with ELX/TEZ/IVA using the patient numbers that were previously agreed for the F/F, F/RF and F/G populations as described in paragraph 6.71. The PBAC considered the number of patients expected to be treated with ELX/TEZ/IVA, applying uptake as outlined in paragraph 6.73, as summarised in Table 28, was reasonable.

7.37 The PBAC advised the sponsor should provide the following information for further consideration:

- Revised estimate of the cost of listing ELX/TEZ/IVA for the F/any population based on the number of treated patients in paragraph 6.74 and the ELX/TEZ/IVA costs per patient per year in paragraph 7.33.
- Revised estimate of cost-offsets based on a TEZ/IVA cost per patient per year of \$ [REDACTED] and an IVA cost per patient per year of \$ [REDACTED].
- Revised expenditure caps for the TEZ/IVA and LUM/IVA RSA and the IVA RSA accounting for the net cost of listing ELX/TEZ/IVA.
- Propose an appropriate MAP to manage the uncertainty associated with the rate of decline in ppFEV₁ over the longer term.

Outcome:

Deferred

8 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.

9 Sponsor's Comment

Vertex is pleased that the PBAC has acknowledged the significant benefits that Trikafta® (elexacaftor/tezacaftor/ivacaftor) can bring to Cystic Fibrosis (CF) patients.

Vertex, along with the CF community, was hopeful for a first time PBAC recommendation for Trikafta, particularly given our involvement in the TGAPBAC Alignment Pilot, which has the overall objective of aligning the regulation and reimbursement process to ensure patients have access to medicines as soon as possible.

Vertex is also disappointed that the long term data provided for LUM/IVA and TEZ/IVA in this submission were not considered by PBAC. These data, from multiple independent sources, clearly substantiate the long term benefits of LUM/IVA and TEZ/IVA and addressed the question of cost-effectiveness of the comparators.

We are committed to continuing to work collaboratively with the PBAC to ensure all eligible patients (estimated 2,200 patients based on the Australian Cystic Fibrosis

Disease Registry Annual Report 2019) who can benefit from treatment have government-funded access to Trikafta as quickly as possible.

Addendum to the March 2021 PBAC Minutes:

4.01 ELEXACAFITOR/TEZACAFITOR/IVACAFITOR

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

10 Background

- 10.1 At its March 2021 meeting, the PBAC deferred its decision about the PBS listing of ellexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) for the treatment of cystic fibrosis (CF) patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene in order to allow engagement with the sponsor to align the proposed listing of ELX/TEZ/IVA, and associated costs and financial implications with the Managed Access Program (MAP) and risk share arrangements (RSA) of the currently listed CFTR modulators, with the cost-effectiveness link with these comparators having not satisfactorily been established by the submission.
- 10.2 Following the March 2021 meeting, the Department and the sponsor engaged in discussions to address the information the PBAC requested for further consideration.

11 Sponsor proposal

- 11.1 The sponsor provided a proposal for the PBAC's consideration.
- 11.2 A comparison of the outstanding matters outlined by the PBAC in March 2021, and the sponsor's proposal is summarised below:

Public Summary Document – March 2021 PBAC Meeting with May 2021 Addendum

PBAC March 2021 deferral advice	May 2021 proposal																																										
Revised estimate of the cost of listing ELX/TEZ/IVA for the F/any population based on the number of treated patients in paragraph 6.74 and the ELX/TEZ/IVA costs per patient per year in paragraph 7.33.	PBAC requested estimates not provided. PBAC requested costs for ELX/TEZ/IVA not proposed. Submission proposed alternate weighted prices and longer timeframe for the initial price. The treated patient estimates in the proposal were similar to those in the March 2021 submission. <i>May 2021 proposal:</i> <table><tr><th></th><th>2021</th><th>2022</th><th>2023</th><th>2024</th><th>2025</th><th>2026</th></tr><tr><td>Total treated patients</td><td>█████¹</td><td>█████¹</td><td>█████¹</td><td>█████¹</td><td>█████¹</td><td>█████¹</td></tr></table> Resulting in net cost of \$800 million to < \$900 million over six years. <i>March 2021 pre-PBAC response:</i> <table><tr><th></th><th>2021</th><th>2022</th><th>2023</th><th>2024</th><th>2025</th><th>2026</th></tr><tr><td>Total treated patients</td><td>█████¹</td><td>█████¹</td><td>█████¹</td><td>█████¹</td><td>█████¹</td><td>█████¹</td></tr></table> Resulting in net cost of \$600 million to < \$700 million over six years. <i>Department estimates based on PBAC March 2021 advice:</i> <table><tr><th></th><th>2021</th><th>2022</th><th>2023</th><th>2024</th><th>2025</th><th>2026</th></tr><tr><td>Total treated patients</td><td>█████¹</td><td>█████¹</td><td>█████¹</td><td>█████¹</td><td>█████¹</td><td>█████¹</td></tr></table> Resulting in net cost of \$100 to million < \$200 million over six years.		2021	2022	2023	2024	2025	2026	Total treated patients	█████ ¹	█████ ¹	█████ ¹	█████ ¹	█████ ¹	█████ ¹		2021	2022	2023	2024	2025	2026	Total treated patients	█████ ¹	█████ ¹	█████ ¹	█████ ¹	█████ ¹	█████ ¹		2021	2022	2023	2024	2025	2026	Total treated patients	█████ ¹	█████ ¹	█████ ¹	█████ ¹	█████ ¹	█████ ¹
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Total treated patients	█████ ¹	█████ ¹	█████ ¹	█████ ¹	█████ ¹	█████ ¹																																					
Revised estimate of cost-offsets based on a TEZ/IVA cost per patient per year of \$█████ and an IVA cost per patient per year of \$█████.	Submission accepted the relevant cost per patient for TEZ/IVA and IVA as basis for estimating the cost-offsets.																																										
Revised expenditure caps for the TEZ/IVA and LUM/IVA RSA and the IVA RSA accounting for the net cost of listing ELX/TEZ/IVA.	Submission appeared to accept general methodology proposed by Department to calculate adjustment to current expenditure caps for the TEZ/IVA and LUM/IVA RSA and the IVA RSA. However, the proposed increase to the TEZ/IVA and LUM/IVA RSA caps is substantially higher due to the submission’s assumptions regarding treated patient numbers and proposed alternate weighted prices and timeframe for the initial price.																																										
Propose an appropriate MAP to manage the uncertainty associated with the rate of decline in ppFEV ₁ over the longer term.	MAP proposed with reference to relative rate of decline beyond one year of listing. Based on Study 105 ██████ follow-up data (year 2 and 3 post-listing) and then on any further available evidence following (year 4 & 5 post-listing).																																										

ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; IVA = ivacaftor; LUM/IVA=lumacaftor/ivacaftor; MAP=Managed Access Program; RSA= risk sharing arrangement; TEZ/IVA = tezacaftor/ivacaftor;
The redacted values correspond to the following ranges:
¹ 500 to < 5,000

11.3 The submission proposed a recalculated weighted initial cost per patient of \$█ vs \$█ as outlined in the PBAC March 2021 advice, and stated that this was

calculated by removing the F/RF population from the economic model. However, the weighted cost per patient for the first 24 weeks in the March 2021 PSD (\$ [REDACTED], paragraph 7.33) was calculated based on the weighting in paragraph 7.32 and an annual cost per patient of \$ [REDACTED] for the F/F population and F/MF populations (paragraph 7.10, paragraph 7.26) and \$ [REDACTED] for the F/RF population and was not based on inclusion of the F/RF population in the economic model. The submission's recalculated annual cost per patient of \$ [REDACTED] was requested for one year of listing. In March 2021, the PBAC had advised the initial weighted cost per patient of \$ [REDACTED] should be implemented for the first 24 weeks of PBS listing only, based on the availability of 24 weeks of comparative data.

- 11.4 The submission did not present estimates based on the PBAC's March 2021 advice and instead proposed similar treated patient estimates to the sponsor's March 2021 submission. The submission's revised estimates resulted in a higher financial impact than presented in its March 2021 pre-PBAC response. This was in part due to a reduction in the value of cost offsets from IVA, LUM/IVA and TEZ/IVA from the proposal's revised approach to calculating the offsets based on the Deeds, compared with the March 2021 submission.
- 11.5 The proposal presented the following revised financial impact of listing ELX/TEZ/IVA, prior to cost offsets associated with existing CFTR modulators.

Table 29: Estimated financial implications of ELX/TEZ/IVA to PBS

Estimated financial implications of ELX/TEZ/IVA	2021	2022	2023	2024	2025	2026
VRTX proposal	\$ [REDACTED] ¹	\$ [REDACTED] ¹	\$ [REDACTED] ¹	\$ [REDACTED] ¹	\$ [REDACTED] ¹	\$ [REDACTED] ¹
VRTX Pre-PBAC response (March 2021)	\$ [REDACTED] ¹	\$ [REDACTED] ¹	\$ [REDACTED] ¹	\$ [REDACTED] ¹	\$ [REDACTED] ¹	\$ [REDACTED] ¹
Department estimates	\$ [REDACTED] ²	\$ [REDACTED] ²	\$ [REDACTED] ²	\$ [REDACTED] ³	\$ [REDACTED] ³	\$ [REDACTED] ³

Source: Table 25, May 2021 ELX/TEZ/IVA proposal

The redacted values correspond to the following ranges:

¹ \$200 million to < \$300 million

² \$100 million to < \$200 million

³ \$90 million to < \$100 million

- 11.6 The proposal presented the following revised net financial impact of ELX/TEZ/IVA, accounting for cost offsets from existing CFTR modulators.

Table 30: Estimated net cost to PBS of listing ELX/TEZ/IVA

Net cost to PBS	2021	2022	2023	2024	2025	2026
New listing	\$ [redacted] ¹	\$ [redacted] ¹	\$ [redacted] ¹	\$ [redacted] ¹	\$ [redacted] ¹	\$ [redacted] ¹
Changed listing	-\$ [redacted] ²	-\$ [redacted] ²	-\$ [redacted] ²	-\$ [redacted] ³	-	-\$ [redacted] ³
Net cost to PBS	\$ [redacted] ³	\$ [redacted] ³	\$ [redacted] ³	\$ [redacted] ³	\$ [redacted] ³	\$ [redacted] ³
<i>Compared to Net cost to PBS:</i>						
VRTX Pre-PBAC response (March 2021)	\$ [redacted] ³	\$ [redacted] ³	\$ [redacted] ³	\$ [redacted] ³	\$ [redacted] ³	\$ [redacted] ³
Department estimates	\$ [redacted] ⁴	\$ [redacted] ⁴	\$ [redacted] ⁵	\$ [redacted] ⁵	\$ [redacted] ⁵	\$ [redacted] ⁶

Source: Table 26 and 27, May 2021 ELX/TEZ/IVA proposal

The redacted values correspond to the following ranges:

¹ \$200 million to < \$300 million² \$90 million to < \$100 million³ \$100 million to < \$200 million⁴ \$30 million to < \$40 million⁵ \$20 million to < \$30 million⁶ \$10 million to < \$20 million

12 PBAC outcome

- 12.1 The PBAC again deferred making a recommendation regarding the proposed listing of elxacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) for the treatment of cystic fibrosis (CF) patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. It did so because the sponsor's revised proposal did not adequately address the parameters outlined in the minutes of the PBAC's March 2021 meeting. The PBAC noted the revised proposal resulted in a net cost to Government that was higher than the proposal put by the sponsor for consideration at the March 2021 meeting.
- 12.2 Overall, the PBAC considered that the revised proposal was not aligned with the PBAC's March 2021 advice as it requested significant deviations with regard to the pricing and financial estimates. However, it deferred completion of its consideration to allow the sponsor to provide further information, outlined in paragraph 12.17 below.
- 12.3 The PBAC recalled the strong consumer support for making ELX/TEZ/IVA available for CF patients as soon as possible, and the importance of the availability of ELX/TEZ/IVA for CF patients that are not able to access other CFTR modulators.
- 12.4 The PBAC noted that the submission had identified a separate subgroup of patients, those with a F/R117H genotype, which had previously been included in the F/not yet characterised subgroup. The PBAC considered it appropriate to remove these patients from the count of F/not yet characterised patients, but did not agree with the submission's proposal that the price for the F/R117H subgroup be the weighted average price of that for the F/F, F/RF and F/MF populations. The PBAC noted that the cost-effectiveness of ELX/TEZ/IVA in the F/R117H group had not been established

and that many patients with F/R117H have residual function and may therefore have a milder phenotype than either the F/F or F/MF populations. Therefore, the PBAC considered it appropriate that the cost per patient in this population should be the same as for the F/RF population.

- 12.5 The PBAC considered the proposal to reallocate 80% of the remaining patients classified as F/not yet characterised in the ACFDR registry to the F/MF population and 20% to the F/RF population was reasonable in the absence of any other data to support the likely subsequent characterisation. The weighting across the populations, including the reallocation, are summarised in Table 3.

Table 31: Proportion of patients within each population

Population (over 12 years of age)	Number of patients in ACFDR analysis	Including reallocation (F/R117H to F/RF, 80% remaining F/not yet to F/MF and 20% to F/RF)	% for calculation of weighted price
F/F	1180	1180	57.5%
F/RF	122	176	8.6%
F/G	166	166	
F/MF	395	610	29.8%
F/not yet	269	-	
F/R117H	85	85	4.1%
Total	2,217	2,217	100.0%

Source: Adapted from Vertex May 2021 proposal, Table 2 - ACFDR data extraction, August 2020 (2019 dataset)

Abbreviations: ACFDR=Australian Cystic Fibrosis Data Registry; F/F = homozygous for F508del-CFTR mutations; F/MF = heterozygous for F508del-CFTR mutation with a second minimal function allele; F/R117H = heterozygous for F508del-CFTR with a second R117H mutation; F/RF = heterozygous for F508del-CFTR with a second residual function mutation; F/not yet= heterozygous for F508del-CFTR mutation that is unknown or not yet characterised;

- 12.6 The PBAC noted the submission's request to maintain the annual cost per patient based on no decline in ppFEV₁ for the first year of listing rather than the first 24 weeks. This was based on data from open-label extension Study 105 which included F/F and F/MF patients. The PBAC recalled direct comparative data were only available for a maximum period of 24 weeks. The PBAC noted the results from the extension study suggested maintenance of ppFEV₁ for up to 48 weeks and considered it was reasonable for the cost per patient specified for the first 24 weeks to be maintained for an additional 24 weeks.

Weighted price calculation for ELX/TEZ/IVA.

- 12.7 Based on the above, the PBAC noted the calculation of the weighted price for ELX/TEZ/IVA would be based on a split of F/F:F/RF:F/R117H:F/MF of 57.5:8.6:4.1:29.8.
- 12.8 The PBAC noted that based on this split that the following weighted costs can be calculated for ELX/TEZ/IVA to remain cost effective:
- An annual cost per patient of \$ [REDACTED] for the supply of ELX/TEZ/IVA for the F/any population for the first year of PBS listing only; and

- An annual cost per patient of \$ [REDACTED] for the supply of ELX/TEZ/IVA for the F/any population for a further 2 years of listing; and
- An annual cost per patient of \$ [REDACTED] for the supply of ELX/TEZ/IVA for the F/any population for any supply beyond 3 years post listing on the PBS.

Table 32: Calculation of weighted cost per patient per year

Population	F/F	F/R117H	F/MF	F/RF	Weighted cost per patient per year ³
% ¹	57.5%	4.1%	29.8%	8.6%	
First year ²	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Further 2 years ²	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Beyond 3 years ²	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

1. Weightings as proposed in paragraph 12.7
2. Costs as proposed in paragraph 7.10 for F/F population and paragraph 7.26 for F/MF population. Costs for F/RF population based on cost-minimisation to TEZ/IVA (as outlined in paragraph 7.17) and costs for F/R117H based on the same cost per patient as for the F/RF population (paragraph 12.4).
3. Calculated

- 12.9 The PBAC noted the proposed MAP for ELX/TEZ/IVA which was intended to address uncertainty associated with the relative rate of decline in ppFEV₁ over the longer term (beyond Year 1 of listing), with data to be provided from the follow-up data from Study 105 and then on any further available evidence. The PBAC recalled its advice from the March 2021 meeting that the proposed listing of ELX/TEZ/IVA, and associated costs and financial implications should be aligned with the MAPs and RSAs of the currently listed CFTR modulators. The PBAC noted the proposed MAP did not align the parameters for listing ELX/TEZ/IVA with those previously agreed for the listed CFTR modulators.
- 12.10 The PBAC noted the proposal for a MAP to determine a price for the F/F and F/MF populations beyond Year 1. The PBAC reiterated the cost per patient approach outlined in paragraph 12.8, which required a lower price beyond Year 1 of listing, was appropriate and any MAP should be based on this pricing structure and address the issues raised in paragraph 7.11 and paragraph 7.27.
- 12.11 The PBAC noted that the revised proposal claimed it was unnecessary for the sponsor to address the scenario of a lower price for LUM/IVA or TEZ/IVA as a potential result of the outcomes of the current MAP in place for these medicines. The sponsor asserted that it believes its submission to the July 2021 meeting demonstrates that there will be no changes to the pricing arrangements. The PBAC noted that it was yet to consider the sponsor's submission in relation to the MAP outcomes for LUM/IVA and TEZ/IVA (scheduled for its July 2021 meeting), and that pre-empting the outcomes of that evaluation process was not appropriate. The PBAC reiterated that it would be appropriate for any reduction in the cost per patient per year of TEZ/IVA as a result of the MAP to flow to ELX/TEZ/IVA such that there is no increase in the ICER.

Financial implications of listing for the F/any population

- 12.12 The PBAC noted that the submission's proposed treated patient numbers had not significantly changed compared with the March 2021 submission's proposed estimates. The PBAC recalled that it had considered the estimated number of treated patients to be overestimated and had advised that a method based on agreed estimates for the current listings of IVA, LUM/IVA and TEZ/IVA would be an appropriate approach to estimating the size of the total treated population with ELX/TEZ/IVA.
- 12.13 The PBAC maintained that estimates for the F/F, F/RF and F/G groups should be based on previously agreed estimates for the listing of the available CFTR modulators on the PBS. While the PBAC acknowledged that previously agreed estimates for IVA, LUM/IVA and TEZ/IVA were based on full time equivalent patients rather than the total eligible patient pool, the PBAC was not minded to change its advice in relation to the estimated patient numbers for these patient populations noting that the current utilisation of LUM/IVA and TEZ/IVA has been lower than estimated at the time of listing. The PBAC acknowledged the use of non PBS-funded CFTR modulator therapies in clinical trials, but considered it unreasonable to assume that there will be no future participation of Australian CF patients in trials of disease-modifying therapies. The PBAC therefore considered that using an epidemiological approach was likely to overestimate uptake and that increasing the estimated treated population for these groups already eligible for CFTR modulator treatment was not sufficiently justified.
- 12.14 The PBAC considered that it may be reasonable for the eligible patients from those populations that are currently ineligible for PBS-listed CFTR modulator therapy (i.e. F/MF and F/R117H groups), to be estimated using an epidemiological approach with reference to the ACFDR current patient numbers. The PBAC accepted the following proposed eligible patient numbers and uptake rates for these groups, noting however that the discontinuation rates applied in the submission (0.99% in F/MF and 0.76% for F/R117H) were extremely optimistic and likely to be higher:
- F/MF: 500 to < 5,000 patients in Year 1 increasing to 500 to < 5,000 patients in Year 6, before uptake (90% in Year 1 increasing to 95% from Year 2 onwards) and discontinuation rates are applied.
 - F/R117H: < 500 patients in Year 1 increasing to < 500 patients in Year 6, before uptake (60% each year) and discontinuation rates are applied

The PBAC recommended maintaining the same assumed discontinuation rates as assumed for LUM/IVA: 6.8% at Year 1 and 14.9% at Year 2.

- 12.15 The PBAC noted the significant financial impact and large opportunity cost of the proposed listing of ELX/TEZ/IVA. While PBAC acknowledged that ELX/TEZ/IVA would be the first available CFTRm therapy for F/MF and F/R117H patients, it was noted that this was not the case for F/F, F/RF and F/G patients.

- 12.16 The PBAC noted that the Department's estimates of the net financial impact to the PBS of the listing of ELX/TEZ/IVA based on the Committee's March 2021 advice was approximately \$100 million to < \$200 million over six years. The PBAC noted that based on its revised advice on the pricing structure (paragraph 12.8), and treated patient estimates for F/MF and F/R117H patients (paragraph 12.14), Department modelling indicated a substantial increase to the net cost of listing, to approximately \$200 million to < \$300 million over six years.
- 12.17 The PBAC advised the sponsor should provide the following information for further consideration:
- Revised estimate of the cost of listing ELX/TEZ/IVA for the F/any population based on the number of treated patients for the F/F, F/RF and F/G populations in paragraph 6.74 of the March 2021 PSD, and the proposed patient numbers for the F/MF and F/R117H populations as per paragraph 12.14; and the ELX/TEZ/IVA costs per patient per year in paragraph 12.8.
 - Revised estimate of cost-offsets based on a TEZ/IVA cost per patient per year of \$ [REDACTED] and an IVA cost per patient per year of \$ [REDACTED].
 - Revised expenditure caps for the TEZ/IVA and LUM/IVA RSA and the IVA RSA accounting for the net cost of listing ELX/TEZ/IVA.
 - A proposal regarding an appropriate MAP, similar to what is in place for the other CFTR modulators, to manage the uncertainty associated with the rate of decline in ppFEV₁ over the longer term.

Outcome:

Deferred

13 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.

14 Sponsor's Comment

Vertex is disappointed that the PBAC has again deferred its decision on the funding of Trikafta (elexacaftor/tezacaftor/ivacaftor), especially given the solutions provided by Vertex to address the points raised in the previous deferral.

Vertex welcomes the PBAC's reappraisal of patient numbers, particularly as the initial assessment from the PBAC was not representative of the number of eligible patients. However, there is still a gap between the PBAC and Vertex's estimates of both eligible and treated patients. Vertex believes the same epidemiological approach using registry data is appropriate for determining the number of all eligible patients regardless of genotype or previous access to treatment, and that the number of treated patients should reflect real world uptake. We remain committed to continuing to work collaboratively with the PBAC to ensure all eligible patients, as identified within the Australian Cystic Fibrosis Data Registry, who could benefit from treatment, have government funded access to Trikafta as quickly as possible.