TAR 461 – Elexacaftor/Tezacaftor/Ivacaftor for the treatment of cystic fibrosis patients over the age of 6 years or 12 years with at least one F508del mutation in the CFTR gene

Date	05/04/2022 (updated 06/2022)
Level of Analysis	Standard

This assessment provides an estimate of the likely cost-effectiveness range of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) for the treatment of cystic fibrosis patients over the age of 6 years, and over the age of 12 years with at least one F508del mutation (F mutation) in the CFTR gene.

A summary of the proposal is provided in the table below.

PROPOSAL OVERVIEW
Pharmaceutical Elexacaftor/tezacaftor/ivacaftor (Trikafta) • 100mg (ELX)/50mg (TEZ)/75mg (IVA) tablet plus 150mg (IVA) • 50mg (ELX)/25mg (TEZ)/37.5mg (IVA) tablet plus 75mg (IVA)
Supplier Vertex Pharmaceuticals Incorporated
Proposed Indication • Cystic fibrosis patients over the age of 6 years with at least one F508del mutation in the CFTR gene. • Cystic fibrosis patients over the age of 12 years with at least one F508del mutation in the CFTR gene.
Dosing • Paediatric and patients <30kg - one tablet in the morning containing 50mg (ELX), 25mg (TEZ), 37.5mg (IVA) and one tablet in the evening containing 75mg (IVA) (approximately 12 hours apart). • Adult and patients >30kg one tablet in the morning containing 100mg (ELX), 50mg (TEZ), 75mg (IVA) and one tablet in the evening containing 150mg (IVA) (approximately 12 hours apart).
Pharmaceutical Price Price per pack - [redacted] (Gross) and [redacted] (Net) [redacted]
PTAC/SPECIALIST ADVISORY COMMITTEE PRIORITY High priority – Respiratory Subcommittee August 2021 (people 6 years and over with CF) & Respiratory Specialist Advisory Committee (SAC) April 2022 Medium priority – PTAC November 2021 (people 12 years and over with CF) Medium priority – PTAC May 2022 (people 6 years and over with CF)
PHARMCONNECT REFERENCE Pharmconnect link – 6 years and older Pharmconnect link – 12 years and older

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An application for the funding of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) for the treatment of people with cystic fibrosis (CF) over the age of 6 years with at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene was received from Vertex in July 2021. Subsequent to the November 2021 Pharmacology and Therapeutics Advisory Committee (PTAC) meeting, Pharmac has also generated a separate proposal for eligible people 12 years and over with CF.

CF is a rare, genetic and progressive disease which causes multisystem organ impairment and premature death. The disease is caused by a defective CFTR protein. A defective CFTR protein results in dysfunctional transport of chloride and other ions across the surface of epithelial cells, which in turn causes a disruption in fluid homeostasis. This leads to the production and retention of thick secretions in multiple organ systems. Build-up of secretions has serious clinical consequences for multiple organs, including the lungs, pancreas, liver, intestine, and reproductive system.

People with CF can experience numerous, serious symptoms which can vary from individual to individual. The most common clinical presentations of the disease include structural lung damage, infection, and inflammation, pancreatic insufficiency, and gastrointestinal complications. People with CF suffer premature mortality, with the life expectancy of a CF patient in New Zealand estimated at 37 years.

ELX/TEZ/IVA is proposed for the treatment of CF in patients aged 6 years and older or 12 years and older who have at least one F508del mutation in the CFTR gene (F/any patients). Current treatment is best supportive care (BSC) for most people with CF, and for people with CF who have an F/Gating mutation, current treatment is BSC plus ivacaftor.

Review of Cost-Utility Analyses

Supplier submission
The application to PHARMAC for the listing of ELX/TEZ/IVA included a cost utility analysis (CUA), which reported a cost utility, in quality adjusted life years (QALYs) per $1 million invested, of [redacted] QALYs/million with a likely range of [redacted]

PHARMAC staff have reviewed the CUA and note issues with the assumed discount rate, treatment adherence, health sector costs and uncertainty of the long-term impact of ELX/TEZ/IVA on lung function decline based on the available evidence. Details are outlined in the supplier model review table – Appendix 1. Pharmac have therefore amended the supplier CUA, by adjusting the discount rate, treatment adherence, health sector costs and the assumed reduction in lung function decline beyond the duration of available evidence.

International cost-utility analyses

International HTA bodies' assessments of ELX/TEZ/IVA were reviewed by Pharmac staff. Summaries of the review are described in Section 3.2.

The Pharmaceutical Benefits Advisory Committee (PBAC) estimated a cost-effectiveness of 1 QALY per million Australian dollars (AUD) for patients with CF 12 years and over for the F/RF subgroup, 2.2 and 2.8 QALY per $ AUD million for F/F and F/MF subgroups, and between 3.9 and 6.5 QALYs per $ AUD million for the F/RF and F/MF subgroups (May 2021). In December 2021 PBAC reported a weighted average cost effectiveness of 2.8 to 6.5 QALYs per million AUD for F/F and F/MF populations.

The Canadian Agency for Drugs and Technologies in Health CADTH estimated a cost-effectiveness of <1 QALY per million Canadian dollars for people with CF 12 years and over with at least one F mutation (September 2021).

In the United States the Institute for Clinical and Economic Review (ICER) estimated a cost-effectiveness of less than 1 QALY/million across all relevant subgroups of patients with CF 12 years and over with at least one F mutation (F/F, F/RF and F/MF subgroups).

Summary of PHARMAC Cost-Utility Analysis

Modifications to the supplier CUA were undertaken by PHARMAC staff to estimate the cost-effectiveness of ELX/TEZ/IVA. The economic model used data derived from Studies 102, 104, 105, 106 and 109, which indicated that patients treated with ELX/TEZ/IVA demonstrated improvements in lung function, patient weight, pulmonary exacerbations and health-related quality of life (HRQOL). ELX/TEZ/IVA was also shown to be well tolerated. The model extrapolates acute outcomes observed in the trials by assuming long term reduction in pulmonary exacerbations and lung function decline, and improved patient survival.

Eligible CF patients 6 years and over
The CUA, in QALYs gained per $1 million invested, of ELX/TEZ/IVA compared to BSC for treating CF in eligible patients 6 years and over, is estimated to be in the range of [redacted]. The CUA result was overall highly inelastic as a result of the high cost of the pharmaceutical and comparatively limited health sector cost offsets. The results of the CUA were most sensitive to: the long-term reduction in lung function decline as a result of ELX/TEZ/IVA treatment, a treatment specific utility increment from ELX/TEZ/IVA, model time horizon and dynamic pricing of ELX/TEZ/IVA. The CUA result was least sensitive to: health state utilities, inpatient pulmonary exacerbation costs, reduced costs of concomitant pharmaceuticals with ELX/TEZ/IVA, treatment adherence rate, pulmonary exacerbation rate reduction with ELX/TEZ/IVA and lung transplant costs.

Eligible CF patients 12 years and over
The CUA result in QALYs gained per $1 million invested, of ELX/TEZ/IVA compared to BSC for treating CF in eligible patients 12 years and over, is estimated to be in the range of [redacted]. The CUA result was overall highly inelastic as a result of the high cost of the pharmaceutical and comparatively limited health sector cost offsets. The results of the CUA were most sensitive to the long-term reduction in lung function decline as a result of ELX/TEZ/IVA treatment, a treatment specific utility increment from ELX/TEZ/IVA, model time horizon and dynamic pricing of ELX/TEZ/IVA. The CUA result was least sensitive to health state utilities, inpatient pulmonary exacerbation costs, reduced cost of concomitant pharmaceuticals with ELX/TEZ/IVA, treatment adherence rate, pulmonary exacerbation rate reduction with ELX/TEZ/IVA and lung transplant costs.

Summary of Budget Impact Analysis

Eligible people with CF 6 years and over
Patient numbers for the 6 years and over patient group were estimated to be 332 in year 1, increasing to 358 in year 5.

The net cost to the hospital pharmaceutical schedule is expected to be [redacted] million in year 1 with a 5-year net present value (NPV) of [redacted] million.

The net cost to DHBs (CPB and other costs) is expected to be [redacted] million in year 1 with a 5-year NPV of [redacted] million. The difference in cost to DHBs compared with the pharmaceutical schedule is driven by savings from reduced hospital admissions and lung transplants.

Eligible people with CF 12 years and over
Patient numbers for the 12 years and over patient group were estimated to be 264 in year 1, increasing to 284 in year 5.

The net cost to the hospital pharmaceutical schedule is expected to be [redacted] million in year 1 with a 5-year net present value (NPV) of [redacted] million.

The net cost to DHBs is expected to be [redacted] million in year 1 with a 5-year NPV of [redacted] million. The difference in cost to DHBs compared with the pharmaceutical schedule is driven by savings from reduced hospital admissions and lung transplants.

1. Proposal Overview

1.1 Population, Intervention, Comparator and outcomes (PICO)

An application for the funding of ELX/TEZ/IVA for the treatment of CF patients over the age of 6 years with at least one F mutation in the CFTR gene was received from Vertex in July 2021. Subsequent to the November 2021 PTAC meeting, Pharmac has also generated a separate proposal for eligible CF patients 12 years and over.

The tables below provides a summary of the patient population; intervention; comparator treatment; and main outcomes of treatment (PICO).

Table 1 – PICO for patients 6 years and over

Population	Cystic fibrosis patients 6 years and over with at least one F508del (F) mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. • F/F • F/MF • F/RF • F/G • F/R117H • F/not yet characterised
Intervention	ELX/TEZ/IVA • Patients <30kg 100mg (ELX), 50mg (TEZ), 75mg (IVA) in the morning and one tablet in the evening containing 75mg (IVA). • Patients >30kg 200mg (ELX), 100mg (TEZ), 150mg (IVA) in the morning and one tablet in the evening containing 150mg (IVA).
Comparator(s) (NZ context)	Patients with at least one F mutation - BSC Patients with at least one F mutation and one gating mutation (F/G) – Ivacaftor + BSC
Outcome(s)	• Lung function (in terms of ppFEV) • Weight-for-age z-score. • Reduced pulmonary exacerbation (PEx) rates. • Reduction in long term decline in ppFEV. • Improved quality of life. • Health sector savings (lung transplants and inpatient costs). • Improved survival.

Table 2 – PICO for CF patients 12 years and over

Population	Cystic fibrosis patients 12 years and over with at least one F508del (F) mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. • F/F • F/MF • F/RF • F/G • F/R117H • F/not yet characterised
Intervention	ELX/TEZ/IVA • 200mg (ELX), 100mg (TEZ), 150mg (IVA) in the morning and one tablet in the evening containing 150mg (IVA).
Comparator(s) (NZ context)	Patients with at least one F mutation - BSC Patients with at least one F mutation and one gating mutation (F/G) – Ivacaftor + BSC

Outcome(s)	• Lung function (in terms of ppFEV) • Weight-for-age z-score. • Reduced pulmonary exacerbation (PEx) rates. • Reduction in long term decline in ppFEV. • Improved quality of life. • Health sector savings (lung transplants and inpatient costs). • Improved survival.

1.2. Patient Population

Description of the disease

CF is a rare, genetic and progressive disease which causes multisystem organ impairment and premature death as a result of a defective CFTR protein. This defective CFTR protein results in defective transport of chloride and other ions across the surface of epithelial cells and causes a disruption in fluid homeostasis. This leads to the production and retention of thick secretions in multiple organ systems. The build-up of secretions has serious clinical consequences for multiple organs including the lungs, pancreas, liver, intestine, and reproductive system. Psychological problems for patients also arise, due to the high associated symptom and treatment burden, and living with a terminal illness from a young age.

The health need of the person

People with CF can experience numerous serious symptoms which can vary from individual to individual. The most common clinical presentations of this disease include structural lung damage, infection, and inflammation, pancreatic insufficiency, and gastrointestinal complications. Patients may also develop comorbidities and complications related to their CF, including liver disease, CF-related diabetes and malnutrition, sinus infections, chronic bone disease (ie osteopenia and osteoporosis), CF-related arthropathy, as well as infertility in males, and to a lesser extent, females.

Structural lung damage begins to manifest in early childhood and is often detected before the onset of symptoms of lung disease. Almost all children with CF aged 4 years and younger show clear structural lung abnormalities including bronchiectasis (the permanent and abnormal widening of the airway due to chronic infection and inflammation), ground glass opacity (a non-specific finding that indicates thickening of the alveolar wall or a partial filling of the air spaces with fluid or solid material), bronchial wall, mucus plugging (build-up of mucus on the airway walls that restricts airflow), consolidation (filling of the air spaces with fluid or solid material) and air trapping. Nearly half of all children with CF aged 6 to 17 have mild-to-severe lung disease. The life expectancy of a CF patient is estimated at 37 years.

Epidemiology

The most common CF mutation in New Zealand is F508del (deletion of the phenylalanine at position 508 of CFTR), which is present in at least one allele in approximately 87.6% of people with CF*(Port CF Data Registry, 2020)*. Over 50% of people with CF are homozygous for the F508del mutation (F/F patients) in New Zealand*(Port CF Data Registry, 2020)* Table 3 summarises the prevalence of F/any patient population in New Zealand by genotype subpopulation.

Table 3 – F/any patient population in New Zealand by genotype subpopulation

Genotype	Number of patients	Proportion of patients
Genotyped patients	**488**	**-**
Patients with at least one *F508del-CFTR* mutation	**430**	**87.6%**
F/F[#]	**241**	**56.0%**
F/RF[#]	**29**	**6.7%**
F/G[#]	**22**	**5.1%**
F/MF[#]	**82**	**19.1%**
F/R117H[#]	**21**	**4.9%**
F/not yet characterised[#]	**35**	**8.1%**

Source: CFNZ Port CF 2020 Data Registry – Pharmac data on file from supplier submission. Note: [#]Proportions are % of population with at least one F508del mutation.
Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; 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.

The F/any patient pool of people with CF aged 6 or 12 years and older consists of six subpopulations based on the patients' genotypes and will be referred to throughout the assessment as:

- **F/F patients**: people who are homozygous for the *F508del-CFTR* mutation (have two copies of *F508del*)
- **F/RF patients**: people who are heterozygous for *F508del* in the *CFTR* gene with a residual function (RF) mutation in the other allele
- **F/G patients**: people who are heterozygous for *F508del* in the *CFTR* gene with a gating (G) mutation in the other allele
- **F/MF patients**: people who are heterozygous for *F508del* in the *CFTR* gene with a minimal function (MF) mutation in the other allele.
- **F/R117H:** are heterozygous for *F508del* in the *CFTR* gene with a *R117H* mutation in the other allele
- **F/not yet characterised**: people 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, RF or MF.

1.3. Current Treatment in New Zealand

Currently, the majority of people with CF receive "best supportive care" (BSC) which includes mucolytics, osmotic agents, antibiotics, bronchodilators, enzyme and vitamin replacements and supplements, and chest physiotherapy. There is minimal impact on the decline in long-term lung function and many patients will suffer episodic exacerbations of their pulmonary disease with BSC.

7 to 8% of people with CF eligible with a class III gating mutation also receive IVA, which, given in combination with best supportive care, addresses the underlying defect and increases CFTR functionality.

The aim with best supportive care is to slow disease progression, maintain respiratory function, improve nutritional status, improve symptoms, and enhance HRQoL. In addition to controlling symptoms, other treatment goals include preserving lung function and improving nutritional status, lowering rate of pulmonary exacerbations requiring antibiotics, and managing co-morbidities such as diabetes.

Bilateral lung transplantation is complex, carries a high mortality risk and is expensive, but it can be appropriate for patients with CF with advanced or severe lung disease that has failed to respond to standard therapy.

1.4. Intervention

Clinical Pharmacology and Mechanism of Action

ELX and TEZ bind to different sites on normal and F508del-CFTR proteins to increase processing and trafficking of the CFTR protein to the epithelial cell surface. IVA potentiates functioning of this CTFR protein by increasing channel gating and enhancing chloride transport (Medsafe, 2021).

ELX/TEZ/IVA is proposed for the treatment of CF in patients aged 6 years and older who have at least one *F508del* mutation in the CF transmembrane conductance regulator (*CFTR*) gene (F/any patients).

Proposed Treatment Paradigm

ELX/TEZ/IVA is intended to be used in conjunction with best supportive care for the treatment of CF in patients aged 6 years or 12 years and older who have at least one *F508del* mutation in the CFTR gene. Patients with CFTR gating mutations can continue taking IVA in conjunction with best supportive care or can switch to ELX/TEZ/IVA plus best supportive care if they carry one *F508del* mutation.

2. Health Benefits

2.1. Clinical Evidence

Table 4 – Evidence summary

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy and safety
Randomised control trials (12 years and older):						
• **Study 102** - efficacy of VX-445 in triple combination (TC) with tezacaftor (TEZ) and ivacaftor (IVA) in subjects with cystic fibrosis (CF) who are heterozygous for F508del and a minimal function mutation (F/MF subjects). ClinicalTrials.gov Identifier: NCT03525444 ○ Middleton et al. N Engl J Med. 2019;381:1809-19 ○ Jain et al. Pediatr Pulmonol. 2019;54:346-47 (conference abstract) ○ Fajac et al. Thorax. 2021;76:A40-1 (conference abstract) ○ CSR available with application documents.						
Study 102	Phase III, randomised, double-blind, active-controlled, parallel-group study	Stable CF patients aged 12 years and older with ppFEV1 between 40% and 90% and who were heterozygous for the F508del in the CFTR gene with a MF mutation (F/MF patients).	201 – ELX/TEZ/IVA 204 - Placebo	ELX/TEZ/IVA – ELX 200 mg, TEZ 100 mg and IVA 150 mg in the morning and IVA 150 mg in the evening, dosed orally 12 hours apart Or Matched oral placebos	24-week intervention period	**Absolute change in ppFEV1 from baseline at Week 4** • ELX/TEZ/IVA 13.6 (95% CI 12.4 to 14.8) • Placebo −0.2 (95% CI −1.3 to 1.0) • Least squares mean (LSM) difference: 13.8 (95% CI 12.1 to 15.4) • *P<0.001* **Absolute change in ppFEV1 from baseline through Week 24** • ELX/TEZ/IVA 13.9 (95% CI 12.8 to 15.0) • Placebo −0.4 (95% CI −1.5 to 0.7) • LSM difference: 14.3 (95% CI 12.7 to 15.8) • P<0.001 **Number of pulmonary exacerbations (PEx) through Week 24** • ELX/TEZ/IVA 41 • Placebo 113 • Rate ratio 0.37 (95% CI 0.25 to 0.55) • P<0.001 **Absolute change in sweat chloride from baseline through Week 24 (mmol/litre)** • ELX/TEZ/IVA −42.2 (95% CI −44.0 to −40.4) • Placebo −0.4 (95% CI −2.2 to 1.4) • LSM difference −41.8 (95% CI −44.4 to −39.3) • P<0.001 **Absolute change in CFQ-R Respiratory Domain score from baseline through Week 24** • ELX/TEZ/IVA 17.5 (95% CI 15.6 to 19.5) • Placebo −2.7 (95% CI −4.6 to −0.8) • LSM difference 20.2 (95% CI 17.5 to 23.0) • P<0.001 **Absolute change in BMI from baseline at Week 24** • ELX/TEZ/IVA 1.13 (95% CI 0.99 to 1.26) • Placebo 0.09 (95% CI −0.05 to 0.22) • LSM difference 1.04 (95% CI 0.85 to 1.23) • P<0.001 **Absolute change in sweat chloride from baseline at Week 4 (mmol/litre)** • ELX/TEZ/IVA −41.2 (95% CI −43.1 to −39.2) • Placebo 0.1 (95% CI −1.9 to 2.0)

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy and safety
						• LSM difference −41.2 (95% CI −44.0 to −38.5) • P<0.001 **Absolute change in CFQ-R Respiratory Domain score from baseline at Week 4 (points).** • Minimally clinically important difference is 4 points • ELX/TEZ/IVA 18.1 (95% CI 15.9 to 20.4) • Placebo −1.9 (95% CI −4.2 to 0.3) • LSM difference 20.1 (95% CI 16.9 to 23.2) • P<0.001 **Adverse events** Patients with at least one adverse event: 93.1% ELX/TEZ/IVA group vs 96.0% in the placebo group Serious adverse events: 13.9% (28) ELX/TEZ/IVA and 20.9% (42) placebo, of which: • 5.4% (11) and 16.4% (33), respectively, were infective pulmonary exacerbation of CF • 1.5% (3) and 0% (0), respectively, were influenza • 1.5% (3) and 0.5% (1), respectively, were rash events • 1.0% (2) and 1.5% (3), respectively, were haemoptysis
• **Study 103** - efficacy of VX-445 in triple combination (TC) with tezacaftor (TEZ) and ivacaftor (IVA) in subjects with cystic fibrosis (CF) who are homozygous for the F508del mutation (F/F). ClinicalTrials.gov Identifier NCT03525548 ○ Heijerman et al. Lancet. 2019;394:1940-48; ○ Majoor et al. North American Cystic Fibrosis Conference. 2020 (Abstract and conference poster, Appendix 1 of Respiratory Subcommittee discussion document). ○ CSR available with application documents						
Study 103	Phase III, randomised, double-blind, active-controlled, parallel-group study	Stable CF patients aged 12 years and older homozygous for F508del-CFTR mutation (F/F patients) and with ppFEV1 between 40% and 90%.	N=107 ELX/TEZ/IVA n=55 TEZ/IVA n=52	ELX/TEZ/IVA – ELX 200 mg, TEZ 100 mg and IVA 150 mg in the morning and IVA 150 mg in the evening, dosed orally 12 hours apart Or TEZ/IVA – TEZ 100 mg in the morning and IVA 150 mg in the evening, dosed orally 12 hours apart	4-week treatment period	**Absolute change from baseline in ppFEV1 at Week 4 (percentage points)** • ELX/TEZ/IVA 10.4 (95% CI 8.6 to 12.2) • TEZ/IVA 0.4 (95% CI -1.4 to 2.3) • LSM difference 10.0 (95% CI 7.4 to 12.6) • P<0.0001 **Absolute change in CFQ-R Respiratory Domain score from baseline at Week 4** • ELX/TEZ/IVA 16.0 (95% CI 12.1 to 19.9) • TEZ/IVA -1.4 (95% CI -5.4 to 2.6) • LSM difference 17.4 (95% CI 11.8 to 23.0) • P<0.0001 **Absolute change in BMI from baseline at Week 4** At week 4, treatment with ELX/TEZ/IVA resulted in a LSM increase in BMI of 0.60 kg/m² (95% CI 0.41 to 0.79; nominal p<0.0001) and a LSM bodyweight increase of 1.6 kg (95% CI 1.0 to 2.1; nominal p<0.0001) compared TEZ/IVA. (analyses not predefined) **Adverse events** Occurred in 32 (58%) participants in the ELX/TEZ/IVA group vs 33 (63%) in the TEZ/IVA group Serious adverse events occurred in two (4%) participants in the ELX/TEZ/IVA

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy and safety
						group (rash in one participant and pulmonary exacerbation in another) and in one (2%) participant in the TEZ/IVA group (pulmonary exacerbation).
Study 103 - HRQoL						**Mean absolute change in CFQ-R non-respiratory domain scores from baseline at week 4 by treatment group** Improvements with ELX/TEZ/IVA compared with TEZ/IVA were seen in 7 of the 11 non-respiratory domain scores, including vitality, physical functioning, and health perceptions
• **Study 105** (rollover from study 102 and 103) - long-term safety and tolerability of VX-445 in triple combination (TC) with tezacaftor (TEZ) and ivacaftor (IVA) in subjects with cystic fibrosis (CF) who are homozygous or heterozygous for the F508del mutation. ClinicalTrials.gov Identifier: NCT03525574 ○ Week 96 analysis Summary and protocol available with application documents						
Study 105	Ongoing Phase III, open-label study	Patients who completed Study 103 (F/F patients) and Study 102 (F/MF patients)	N=507 F/F patients n=107 F/MF patients n=403	ELX/TEZ/IVA – ELX 200 mg, TEZ 100 mg and IVA 150 mg in the morning and IVA 150 mg in the evening, dosed orally 12 hours apart	192-week follow-up (96-week analysis presented)	**F/F patients: from study 103** **Absolute change from baseline in ppFEV1 (% points)** • TEZ/IVA in Study 103 then ELX/TEZ/IVA in Study 105 – LSM 12.4 (95% CI 9.6 to 15.1) • ELX/TEZ/IVA in Study 103 then ELX/TEZ/IVA in Study 105 – LSM 11.5 (95% CI 8.8 to 14.2) **Absolute change from baseline in sweat chloride (mmol/L)** • TEZ/IVA in Study 103 then ELX/TEZ/IVA in Study 105 – LSM -48.3 (95% CI -53.7 to -42.8) • ELX/TEZ/IVA in Study 103 then ELX/TEZ/IVA in Study 105 – LSM -49.7 (95% CI -55.0 to -44.4) **Number of pulmonary exacerbations (PEx)** • Overall 35/107 patients with events. • Estimated event rate per year 0.21 (95% CI 0.14 to 0.30) **Absolute change from baseline in CFQ-R Respiratory Domain Score (points)** • TEZ/IVA in Study 103 then ELX/TEZ/IVA in Study 105 – LSM 15.6 (95% CI 11.0 to 20.1) • ELX/TEZ/IVA in Study 103 then ELX/TEZ/IVA in Study 105 – LSM 18.0 (95% CI 13.6 to 22.5) **Absolute change from baseline BMI (kg/m^2)** • TEZ/IVA in Study 103 then ELX/TEZ/IVA in Study 105 – LSM 1.28 (95% CI 0.80 to 1.76) • ELX/TEZ/IVA in Study 103 then ELX/TEZ/IVA in Study 105 – LSM 1.50 (95% CI 1.03 to 1.96) **F/MF patients: from study 102** **Absolute change from baseline in ppFEV1 (% points)** • Placebo in study 102 then ELX/TEZ/IVA in Study 105 – LSM 15.2 (95% CI 13.6 to 16.7) • ELX/TEZ/IVA in study 102 then ELX/TEZ/IVA in Study 105 – LSM 14.3 (95% CI 12.7 to 15.8) **Absolute change in sweat chloride (mmol/L)** • Placebo in study 102 then ELX/TEZ/IVA in Study 105 – LSM -48.6 (95% CI -51.3 to -45.8)

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy and safety
						• ELX/TEZ/IVA in study 102 then ELX/TEZ/IVA in Study 105 – LSM -45.8 (95% CI -48.5 to -43.0) **Number of pulmonary exacerbations (PEx)** • Overall 136/403 subjects with events (253 events total) • Estimated event rate per year 0.21 (95% CI 0.17 to 0.26) **Absolute change from baseline in CFQ-R Respiratory Domain Score (points)** • Placebo in study 102 then ELX/TEZ/IVA – LSM 20.1 (95% CI 17.5 to 22.6) • ELX/TEZ/IVA in study 102 then ELX/TEZ/IVA – LSM 21.7 (95% CI 19.1 to 24.2) **Absolute change from baseline BMI (kg/m^2)** • Placebo in study 102 then ELX/TEZ/IVA – LSM 1.87 (95% CI 1.61 to 2.13) • ELX/TEZ/IVA in study 102 then ELX/TEZ/IVA – LSM 1.58 (95% CI 1.32 to 1.84) **Safety (N=506; Study 105, F/F and F/MF)** • Number of AEs (Total): 6547 • Subjects with Grade 3/4 AEs: 84 (16.6%) • Subjects with SAEs: 126 (24.9%) • Subjects with related SAEs: 15 (3.0%) • Subjects with AEs leading to death: 1 (0.2%) Source: 105 CSR 96-Week Analysis May 2021 p24
• **Study 104** - efficacy, safety and pharmacodynamics of elexacaftor (ELX, VX-445) in triple combination (TC) with tezacaftor (TEZ) and ivacaftor (IVA) in subjects with cystic fibrosis (CF) who are heterozygous for F508del and a gating or residual function mutation (F/G and F/RF genotypes). ClinicalTrials.gov Identifier: NCT04058353 ○ Barry et al. N Engl J Med. 2021;385:815-25 (Appendix B) ○ CSR available with application documents						
Study 104	Phase III double-blind, randomised, active-controlled trial	CF patients aged 12 years or older heterozygous for F508del and a gating or residual function mutation (F/G and F/RF genotypes)	N=258	ELX/TEZ/IVA (n=132) or active control (either IVA or TEZ/IVA n=126)	8 weeks	**Total group** **Absolute change from baseline in ppFEV1 (% points)** • ELX/TEZ/IVA LSM 3.7 (95% CI 2.8 to 4.6) • Active control LSM 0.2 (95% CI -0.7 to 1.1) ○ Between-group difference 3.5 % points (95% CI 2.2 to 4.7) **Absolute change in sweat chloride (mmol/L)** • ELZ/TEZ/IVA LSM -22.3 (95% CI -24.5 to -20.2) • Active control LSM 0.7 (95% CI -1.4 to 2.8) ○ Between-group difference -23.1 (95% CI -26.1 to -20.1) **Absolute change from baseline in CFQ-R Respiratory Domain Score (points)** • ELX/TEZ/IVA LSM 10.3 (95% CI 8.0 to 12.7) • Active control LSM 1.6 (95% CI -0.8 to 4.1)

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy and safety
						○ Between-group difference 8.7 (95% CI 5.3 to 12.1) **<u>Subgroup - F508del-gating genotypes</u>** **Absolute change from baseline in ppFEV1 (% points)** • ELX/TEZ/IVA LSM 5.8 (95% CI 4.2 to 7.4) • Active control LSM 0.1 (95% CI -1.6 to 1.7) ○ Between-group difference 5.8 (95% CI 3.5 to 8.0) **Absolute change in sweat chloride (mmol/L)** • ELZ/TEZ/IVA LSM -21.8 (95% CI -25.7 to -17.8) • Active control LSM -1.8 (95% CI -5.7 to 2.2) ○ Between-group difference -20.0 (95% CI -25.4 to -14.6) **Absolute change from baseline in CFQ-R Respiratory Domain Score (points)** • ELX/TEZ/IVA LSM 10.2 (95% CI 6.6 to 13.8) • Active control LSM 1.3 (95% CI -2.5 to 5.2) ○ Between-group difference 8.9 (95% CI 3.8 to 14.0) **<u>Subgroup - F508del-residual function genotypes</u>** **Absolute change from baseline in ppFEV1 (% points)** • ELX/TEZ/IVA LSM 2.5 (95% CI 1.4 to 3.5) • Active control LSM 0.5 (95% CI -0.5 to 1.5) ○ Between-group difference 2.0 (95% CI 0.5 to 3.4) **Absolute change in sweat chloride (mmol/L)** • ELZ/TEZ/IVA LSM -23.1 (95% CI -25.6 to -20.6) • Active control LSM 1.7 (95% CI -0.9 to 4.3) ○ Between-group difference -24.8 (95% CI -28.4 to -21.2) **Absolute change from baseline in CFQ-R Respiratory Domain Score (points)** • ELX/TEZ/IVA LSM 10.4 (95% CI 7.2 to 13.7) • Active control LSM 1.9 (95% CI -1.4 to 5.1) ○ Between-group difference 8.5 (95% CI 4.0 to 13.1) **<u>Adverse events</u>** • Any AE: 66.7% (88) ELZ/TEZ/IVA vs 65.9% (83) Active control • Serious AEs: 3.8% (5) ELZ/TEZ/IVA vs 8.7% (11) Active control; of which 1.5% and 5.6%, respectively, were infective pulmonary exacerbation of cystic fibrosis Most common AEs: • Headache: 8.3% ELZ/TEZ/IVA vs 15.1% Active control • Abdominal pain: 5.3% ELZ/TEZ/IVA vs 1.6% Active control

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy and safety
						• Cough: 2.3% ELZ/TEZ/IVA vs 14.3% Active control • Infective pulmonary exacerbation of cystic fibrosis: 2.3% ELZ/TEZ/IVA vs 10.3% Active control • Any AE involving rash: 3.0% ELZ/TEZ/IVA vs 4.0% Active control • Any AE involving elevated aminotransaminase levels: 6.1% ELZ/TEZ/IVA vs 0.8% Active control
Clinical trials (6-11 years)						
• **Study 106** - pharmacokinetics (PK), safety, tolerability, efficacy, and pharmacodynamic effect of VX-445, tezacaftor (TEZ), and ivacaftor (IVA) when dosed in triple combination (TC) in Cystic Fibrosis (CF) subjects 6 through 11 years of age with F/F and F/MF genotypes. ClinicalTrials.gov Identifier: NCT03691779 ○ Zemanick et al. Am J Respir Crit Care Med. 2021;203:1522-32; ○ CSR available with application documents						
Study 106 (part B)	Phase III, 24-week open-label study	Stable CF patients aged 6 through 11 years of age who weighed ≥15 kg and with FEV1 ≥40% of predicted normal for age, sex and height using equations of the Global Lung Function Initiative at the Screening Visit. Subjects who are homozygous for F508del (F/F genotype) or heterozygous for F508del and an MF mutation that is not responsive to IVA and TEZ/IVA (F/MF genotype)	N=16 – Part A N=66 – Part B	Part A: ELX 100 mg, TEZ 50 mg and IVA 75 mg in the morning and IVA 75 mg in the evening, dosed orally 12 hours apart Part B: <30 kg: ELX 100 mg, TEZ 50 mg and IVA 75 mg in the morning and IVA 75 mg in the evening, dosed orally 12 hours apart ≥30 kg: ELX 200 mg, TEZ 100 mg and IVA 150 mg in the morning and IVA 150 mg in the evening, dosed orally 12 hours apart	15 days of treatment in Part A and 24 weeks of treatment in Part B. Subjects who participated in Part A could participate in Part B.	**F/F patients receiving ELX/TEZ/IVA** **Absolute change from baseline in ppFEV1 (% points)** • LSM 11.2 (95% CI 7.2 to 15.2; P<0.0001) **Absolute change in sweat chloride (mmol/L)** • LSM -70.4 (95% CI -75.6 to -65.3; P<0.0001) **Absolute change from baseline in CFQ-R Respiratory Domain Score (points)** • LSM 7.0 (95% CI 3.9 to 10.1) **Absolute change from baseline in LCI2.5 (lung clearance index)** • LSM -1.64 (95% CI -2.34 to -0.94) **F/MF patients receiving ELX/TEZ/IVA** **Absolute change from baseline in ppFEV1 (% points)** • LSM 9.1 (95% CI 6.3 to 11.9; P<0.0001) **Absolute change in sweat chloride (mmol/L)** • LSM -55.1 (95% CI -59.0 to -51.2; P<0.0001) **Absolute change from baseline in CFQ-R Respiratory Domain Score (points)** • LSM 6.9 (95% CI 3.2 to 10.6; P=0.0005) **Absolute change from baseline in LCI2.5 (lung clearance index)** • LSM -1.72 (95% CI -2.11 to -1.33; P<0.0001) **F/F and F/MF patients receiving ELX/TEZ/IVA** **Absolute change from baseline in ppFEV1 (% points)** • LSM 10.2 (95% CI 7.9 to 12.6; P<0.0001) **Absolute change in sweat chloride (mmol/L)** • LSM -60.9 (95% CI -63.7, -58.2; P<0.0001) **Absolute change from baseline in CFQ-R Respiratory Domain Score (points)** • LSM 7.0 (95% CI 4.7 to 9.2; P<0.0001) **Absolute change from baseline in LCI2.5 (lung clearance index)** • LSM -1.71 (95% CI -2.11 to -1.30; P<0.0001) **Adverse events (Part B, N=66)** • Total AEs: 341

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy and safety
						• Subjects with AEs leading to study drug discontinuation: 1 (1.5) • Subjects with AEs leading to study drug interruption: 1 (1.5) • Subjects with Grade 3/4 AEs: 1 (1.5) • Subjects with SAEs: 1 (1.5) • Subjects with AEs leading to death: 0 Source: 105 CSR 96-Week Analysis May 2021 p24, Study 106 CSR Table 12-4 p105

Pex, new or change in antibiotic therapy (IV, inhaled, or oral) for any four or more of signs/symptoms (change in sputum, new or increased haemoptysis, increased cough, increased dyspnoea, malaise, fatigue or lethargy, temperature above 38°C (equivalent to approximately 100.4°F) anorexia or weight loss, sinus pain or tenderness, change in sinus discharge, change in physical examination of the chest, decrease in pulmonary function by 10 percent, radiographic changes indicative of pulmonary infection.

Abbreviations: ppFEV1, percent predicted Forced Expiratory Volume in 1 second, PEx, Pulmonary Exacerbation, CFQ-R, Cystic Fibrosis Questionnaire Revised, BMI, Body Mass Index, LCI25, Lung Clearance index 2.5%, AE, adverse event; ELX, elexacaftor; IVA, ivacaftor; LSM, least squares mean; SAE, serious adverse event; TEZ, tezacaftor.

2.2 Review of Clinical Evidence

Respiratory Subcommittee August 2021 & Respiratory Specialist Advisory Committee (SAC) April 2022

The Subcommittee recommended that elexacaftor/tezacaftor/ivacaftor be listed with a high priority within the context of treatment for respiratory disease in 2021 and in 2022, that no change be made to their previous recommendation.

In making their recommendation in 2021 the Subcommittee noted:

- the significant health need for cystic fibrosis patients aged 6 years and older in New Zealand for whom there are no funded CFTR modulator therapies
- the strong evidence of benefit of elexacaftor/tezacaftor/ivacaftor in patients with at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.
- In making this recommendation, the Subcommittee also noted the exceptionally high cost of elexacaftor/tezacaftor/ivacaftor for this patient group and that it would have a significant impact on the Combined Pharmaceutical Budget if funded.

Pharmacology and Therapeutics Advisory Committee (PTAC) November 2021 & PTAC May 2022

In November 2021 the Committee recommended that ELX/TEZ/IVA be listed with a **medium priority** for patients aged 12 years and older who have at least one F508del mutation in the CF transmembrane conductance regulator (CFTR) gene.

In November 2021 the Committee recommended that ELX/TEZ/IVA for the treatment of CF patients aged less than 12 years of age who have at least one F508del mutation in the CF transmembrane conductance regulator (CFTR) gene be **deferred** pending the availability of further data supporting the evidence of efficacy of ELX/TEZ/IVA for patients less than 12 years of age. In making their recommendation the Committee noted:

- the high health need of this population and the apparent rapid benefit of ELX/TEZ/IVA for CF patients, however considered that there is a lack of longer-term evidence of benefit in this patient group.

- The lack of published evidence supporting the efficacy of ELX/TEZ/IVA for CF patients less than 12 years of age or in patients with mutations responsive in vitro to ELX/TEZ/IVA.
- The substantial cost of this treatment for this patient group and the impact that funding this treatment may have on the Combined Pharmaceutical Budget.

In May 2022, the Committee recommended that ELX/TEZ/IVA be listed with a medium priority for patients aged six years and older who have at least one F508del mutation in the CF transmembrane conductance regulator (CFTR) gene.

- In making these recommendations, the Committee noted the Respiratory Advisory Committee responses to PTAC's previous considerations in April 2022, and the supplementary information provided by the supplier and clinicians experienced in the treatment of cystic fibrosis. The Committee noted the early evidence of benefit of ELX/TEZ/IVA and acknowledged the benefit of early treatment of cystic fibrosis in preventing long term sequelae. The Committee however considered that there was significant uncertainty regarding the long-term outcomes that could be expected with ELX/TEZ/IVA and the high cost of ELX/TEZ/IVA.

3. Supplier and International Cost-Utility Analyses

3.1 Cost-Utility Analysis in Application

The application to PHARMAC for the listing of ELX/TEZ/IVA included a CUA, which reported a cost-utility of [redacted] QALYs/million with a range of [redacted].

PHARMAC staff have reviewed the CUA and note issues with the assumed discount rate, treatment adherence, health sector costs and uncertainty of the long-term impact on lung function decline based on the available evidence, details are outlined in the supplier model review table – Appendix 1. PHARMAC have therefore amended the supplier CUA making adjustments to the discount rate, treatment adherence, health sector costs and the assumed reduction in lung function decline beyond the available evidence.

3.2 International Cost-Utility Analyses

CADTH
An estimate of the cost-effectiveness of ELX/TEZ/IVA for people with CF 12 years and over with at least one F mutation were published by the Canadian Agency for Drugs and Technologies in Health (CADTH) in September 2021 (CADTH, 2021). The base-case CUA result, in QALYs per $1 million Canadian dollars (CAD) invested, was estimated to be less than 1 QALY/million across all relevant subgroups. Consequently, CADTH recommended a price reduction of at least 90% of the gross price, to allow the proposal to be considered cost-effective at a willingness to pay threshold of $50,000 CAD per QALY.

PHARMAC staff note that CADTH also made the following adjustments to the CUA assumptions in their economic assessment: removal of an additional benefit of ELX/TEZ/IVA on the long-term rate of decline in percent predicted forced expiratory volume (ppFEV1) and pulmonary exacerbations, the removal of dynamic pricing of ELX/TEZ/IVA, the inclusion of costs for ELX/TEZ/IVA in the period for which it achieved a survival benefit in comparison with BSC, the removal of an adjustment to drug acquisition costs by patient compliance, and, the removal of a treatment-specific utility increment for patients receiving ELX/TEZ/IVA.

PBAC
An estimate of the cost-effectiveness of ELX/TEZ/IVA for people with CF 12 years and over with at least one F mutation was published by the Pharmaceutical Benefits Advisory Committee (PBAC) with an addendum in May 2021 (PBAC, March 2021). PBAC's base case ICER estimates were in the range of 6.45 to 7.4 QALYs per $ million AUD for the F/F genotype subgroup and between 3.9 and 6.5 QALYs per $million for the F/RF and F/MF subgroups. Revised ICER estimates based on ESC recommendations for a multivariate sensitivity analysis, were reported to be between 2.2 and 2.8 QALY per $ million AUD for F/F and F/MF subgroups and between 0.95 and 1 QALY per $ million AUD for the F/RF subgroup.

Pharmac staff note the PBAC assessment was based on a mixed comparator of TEZ/IVA for F/F and F/RF and BSC for F/MF populations. PHARMAC staff note that PBAC recommended the adjustment of the following assumptions - adjustment of an additional benefit of ELX/TEZ/IVA on the relative rate of decline in ppFEV1 from 61.5% to 42%; removal of treatment specific utility benefit for ELX/TEZ/IVA (base case 0.08) and the same price for ELX/TEZ/IVA and TEZ/IVA throughout the model time horizon (i.e. no reduction due to LoE).

In December 2021 the PBAC received a resubmission from the supplier which was broadly consistent with the submission received in March 2021, with the exception of the relative rate of decline in ppFEV for ELX/TEZ/IVA (PBAC, December 2021). Subsequent to reviewing further long-term evidence from Study 105, PBAC agreed with the supplier's resubmission estimate for the relative rate of decline in ppFEV1 for ELX/TEZ/IVA increasing from 61.5% to 80%.

An updated weighted average ICER range was reported for F/F and F/MF populations ranging from $155,000 and $355,000 AUD, equivalent to 2.82 to 6.45 QALYs per $ million AUD.

ICER
An estimate of the cost-effectiveness of ELX/TEZ/IVA for people with CF 12 years and over with at least one F mutation (F/F, F/RF and F/MF subgroups) was published by the Institute for Clinical and Economic Review (ICER) in September 2020 (TICE et al, 2020). The base-case CUA in QALYs per US$1 million invested was estimated to be less than 1 QALY/million across all relevant subgroups. As a result, ICER recommended a discount of 80% to 83% (Table ES7) of the gross price for ELX/TEZ/IVA to be considered cost-effective at a willingness to pay threshold of $50,000 USD per QALY.

Pharmac staff note the ICER assessment was based on a BSC comparator. PHARMAC staff note that ICER found the CUA result most sensitive to the following assumptions: additional benefit of ELX/TEZ/IVA on the long-term rate of decline in ppFEV1 and the pharmaceutical cost of ELX/TEV/IVA. The ICER assessment found the CUA result insensitive to varying the estimates for utilities, reduction in acute pulmonary exacerbations, costs of acute pulmonary exacerbations, gains in ppFEV1, transplant costs, and the costs of best supportive care

4. PHARMAC Cost-Utility Analysis

The supplier's CUA was amended to estimate the cost-effectiveness of ELX/TEZ/IVA for CF patients over 6 years and over with at least one F mutation (F/any) in the CFTR gene. Details of this CUA are shown in Table 5.

Key changes to the supplier model, in the base case of the amended Pharmac model, include:

- discount rate changed from 1.03% to 3.5% as per the Prescription for Pharmacoeconomic analysis v2.2 (Pharmac, 2015)
- change in the long-term reduction in lung function decline from 80% across all individuals in the model to 90% for people with a baseline ppFEV1 ≥70% and 65% for people with a baseline ppFEV1 <70%
- change in the utility for the CF health states from the supplier submitted utility estimates by clinician proxy to estimates based on patient-reported HRQOL
- increase in adherence rate from 90% to 95%
- adjustment of health sector costs to be most relevant to New Zealand by utilising event rates from an Australian study (van Gool et al, 2013) and applying New Zealand-specific health sector costs based on the Pharmac Cost and Resource Manual 2018
- assumption that ELX/TEZ/IVA would reduce BSC pharmaceutical costs

Table 5 – Key components of the cost-utility analysis

Component	Description
Type(s) of analysis	Cost-utility analysis (base case)
Outcomes	Quality-adjusted life-years (base case)
Time horizon	Lifetime (base case)
Method(s) used to generate results	Individual patient microsimulation
Health states	Normal, Mild, Moderate and Severe CF, Post lung transplant and Death
Cycle length	First two years of analysis: 4-Week cycle length From two years onward: 52-Week cycle length
Comparator	Best supportive care
Transition probabilities	Treatment effects based on pivotal RCT evidence and ITCs (e.g. improved ppFEV$_1$; reduced PExs; improved weight-for-age z-scores; [Study 102, Study 104, Study 106, Study 109, ITC Appendix of supplier submission]). Baseline ppFEV$_1$ decline based on large longitudinal registry analyses (Konstan *et al.* 2007, de Boer *et al.* 2011, Sawicki *et al.* 2017). Long-term reduction in the rate of ppFEV$_1$ decline associated with CFTR modulator treatment based on an Interim Analysis of Study 105 (Study 105 Week 96 Summary and TFLs; data cutoff date: 25 March 2021 – Pharmac data on file from supplier submission). Baseline hazard function for survival derived from parametric survival function that most appropriately fit the survival data from UK CF data registry. Individual patient characteristics (baseline values from the pivotal RCTs) were related to survival through a Cox proportional hazards model (Liou *et al.* 2001) which identified nine key characteristics of patients with CF that were found to predict survival: age, ppFEV$_1$, gender, weight-for-age z-score, pancreatic insufficiency, diabetes, *Staph aureus* [Sa] infection, *Burkholderia cepacia* [Bc] infection, and number of acute exacerbations per year.
Software	Microsoft Excel using Visual Basic.

Abbreviations: ITC – indirect treatment comparison; RCT – randomised controlled trial.
As adapted from (Vertex Pharmaceuticals - Economic model report, 2021)

4.1 Scope of Analysis

The analysis was undertaken from the perspective of the funder, with regards to PHARMAC's Factors for Consideration.

4.1.1 Target Population and comparator

The evaluation presents three CUAs. The three CUAs compare ELX/TEZ/IVA treatment with BSC for patients with CF aged 6 years or 12 years and over, for the following genotype groupings, with proportions in (%):

- CUA 1: F/F patients (59.1%)
- CUA 2: F/MF patients (25.4%)
- CUA 3: F/RF patients (15.5%)

Results of the CUA are presented as a weighted average CUA result of the three modelled subgroups.

The genotype proportions in the model have been calculated using the genotype proportions reported by the Port CF data registry outlined in Table 6 (Port CF Data Registry, 2020). To calculate the relative proportion of F/MF and F/RF genotypes in the model, F/R117H have been assumed to be included as an F/RF genotype and 38% of F/not yet characterised assumed to be F/RF and 62% assumed to be F/MF. The 38:62 split of F/not yet characterised patients redistributed as F/RF and F/MF genotypes respectively, is based on the relative proportion of F/RF and F/MF genotypes.

Pharmac notes that the F/Gating genotypes were not included in the supplier model, which may underestimate the weighted cost effectiveness result, though this is likely to be immaterial owing to the relatively small proportion of people with an F/Gating mutation expected to take up treatment (~4%).

Table 6 – Genotype proportions in the CUA model

Genotype	Patient numbers	Proportion in model
F/F	241	59.1%
F/RF*	63	15.5%
F/MF**	104	25.4%
Total	408	100%

**Includes 29 F/RF patients, 21 F/R117H patients and 38% of F/not yet characterised patients.*
*** Includes 82 F/MF patients and 62% of F/not yet characterised patients.*

4.2 Model Structure

An individual state-transition patient simulation model was submitted by the supplier, modified by Pharmac staff, and used to evaluate the cost-effectiveness of ELX/TEZ/IVA used in combination with BSC for the treatment of CF in patients aged ≥6 years or ≥12 years with at least one F508del mutation in the CFTR gene. In all mutation subgroups, ELX/TEZ/IVA is compared with BSC (CUA 1, CUA 2, and CUA 3).

4.2.1 Time Horizon

A lifetime time horizon was adopted to capture all major differences in clinical and cost outcomes between the intervention and comparator treatments.

For the first two years, four-week cycles are used, to capture shorter-term outcomes observed in the relevant clinical trials, and annual cycles thereafter.

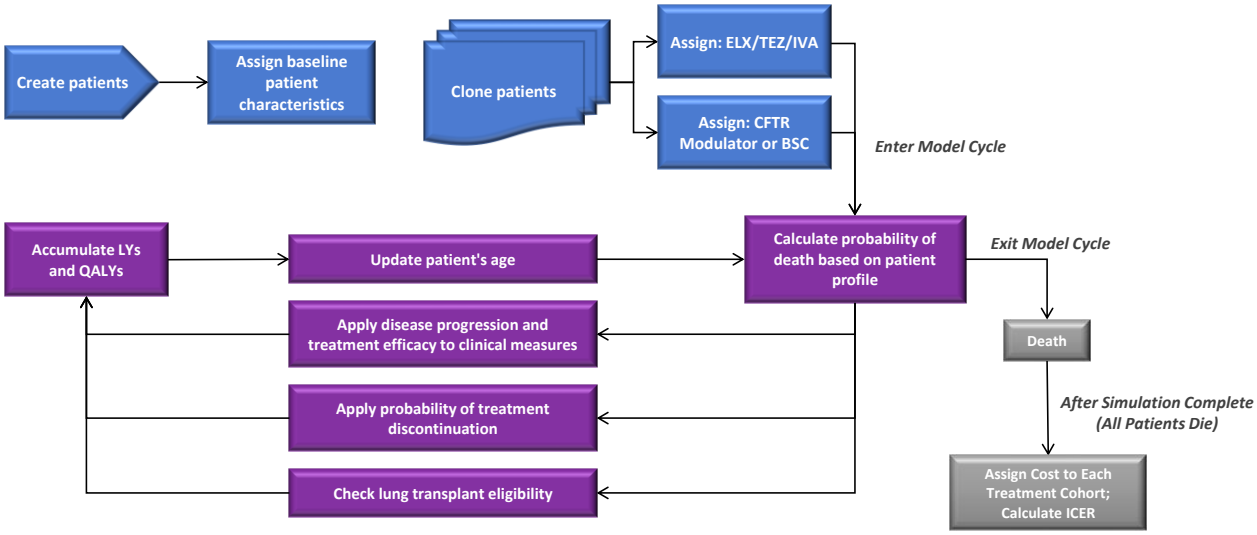
All costs and benefits were discounted at 3.5%.

4.2.2 Model Structure

As shown in Figure 1, the microsimulation is used to capture the heterogeneity in CF disease progression and treatment benefits for individual patients over time. For each comparison, two cohorts with identical baseline characteristics are simulated to estimate the costs and outcomes for patients treated with ELX/TEZ/IVA and for the comparator – BSC. The genotype-specific simulated cohorts are derived from individual patient-level baseline data collected in the clinical trials of ELX/TEZ/IVA. A total of 2,000 patient profiles are simulated for each treatment cohort, as this is the number of profiles needed to achieve stable model outputs (i.e., a negligible change in the cohort-level result was seen across iterations, when simulating beyond 2,000 patients) (Vertex Pharmaceuticals - Economic model report, 2021). Using identical cohorts ensures that any differences in modelled outcomes between the two cohorts

are attributable to the treatment benefit modelled, rather than to differences in patient baseline characteristics.

Figure 1 – Model structure



Adapted from (Vertex Pharmaceuticals - Economic model report, 2021).

4.3 Transformation and Extrapolation of Clinical Evidence

To predict the long-term effects of ELX/TEZ/IVA treatment on patient morbidity and mortality, key patient characteristics have been extrapolated beyond the period of the pivotal RCTs in the economic analysis. This Section describes the methods used to extrapolate the following patient characteristics in the economic model:

- ppFEV1
- weight-for-age z-score
- pulmonary exacerbations

Treatment effects for ELX/TEZ/IVA are derived from the relevant pivotal Phase 3 trials for each mutation subgroup and their corresponding open-label extension studies, including: F/F (Study 106 & Study 109; CUA 1), F/MF (Study 106 & Study 102; CUA 2), and F/RF (Study 104; 3.3.3 TRI Study 104 ITC; CUA 3) populations.

Simulated patient age, ppFEV1, PEx, WFAZ and CF-related diabetes (CFRD) status are updated at the beginning of each model cycle. Gender, pancreatic sufficiency, and respiratory infection status are assumed to remain unchanged from baseline and are not impacted by treatment; therefore, these characteristics are not tracked over the duration of the model. Age and CFRD are updated at the beginning of each cycle but are not affected by assigned treatment. ppFEV1, annual number of PEx, and weight-for-age z-score are updated each cycle and may differ between clones based on the treatment received (Vertex Pharmaceuticals - Economic model report, 2021).

Acute and long-term improvement in lung function (ppFEV1)

ELX/TEZ/IVA is assumed to impact ppFEV1 in two ways: (1) an acute increase in ppFEV1 immediately after treatment initiation, and (2) a slowing of the rate of ppFEV1 decline over the longer-term. It has been assumed that patients with ELX/TEZ/IVA have an initial/acute increase in ppFEV1 from baseline, outlined in Table 7.

Data were not available in the F/RF population for ELX/TEX/IVA, so the percentage point difference from an ITC (which included Study 104), 1.9, was summed with the percentage increase in ppFEV1 of ELX/TEZ/IVA relative to BSC from Study VX-16-661-115 (least squares mean change of 2.8) to estimate acute increase in ppFEV1 in this group. The supplier's method subject to critical appraisal owing to the very small proportion of the overall patient group in the F/RF subgroup.

Table 7 – Acute increase in ppFEV1 (relative to BSC).

Age strata (at initiation)	Outcome/s	F/F		F/MF		F/RF	
		ELX/TEZ/IVA	BSC	ELX/TEZ/IVA	BSC	ELX/TEZ/IVA	BSC
6-11	$ppFEV_1$ (time)	11.2% (24 weeks)	No change (24 weeks)	9.1% (24 weeks)	No change (24 weeks)	4.7% (8 weeks)	No change (8 weeks)
12+		14.1% (24 weeks)	No change (24 weeks)	14.3% (24 weeks)	No change (24 weeks)	8.7% (8 weeks)	No change (8 weeks)

Sources: F/F: [Study 106, 109 & ITC Appendix]; F/MF: [Study 102, 106]; F/RF: [Study 104 & ITC Appendix] (Vertex Pharmaceuticals - Economic model report, 2021)

Long-term decline in $ppFEV_1$: baseline decline – adapted from (Vertex Pharmaceuticals - Economic model report, 2021)

CUA 1–2: F/F and F/MF

The baseline rate of ppFEV1 decline in patients treated with BSC alone in CUA 1 and 2 (i.e., those with F/F and F/MF CFTR mutations) is taken from two studies. The first, Konstan et al. (2007), was a prospective study to characterise the natural history of the pulmonary disease and growth in the paediatric and adolescent populations with CF (Konstan et al, 2007). This study was based on the Epidemiologic Study of CF registry in North America. Data were collected from 1994 to 2005. This study reported mean rates of ppFEV1 decline by age group (see Table 8).

The second study, by de Boer et al. (2011), was used to provide a rate of ppFEV1 decline for adults (see Table 8) (De Boer et al, 2011). de Boer et al. (2011) used evidence from a three-year prospective observational cohort study to analyse the associations between pulmonary exacerbations and ppFEV1 decline, and accelerated time to death and lung transplantation, in CF adult patients attending CF clinics in Ontario, Canada. A total of 446 patients were included in this study. The ppFEV1 decline rates and the mean duration of follow-up (categorised by the number of exacerbations per year) were used to calculate a weighted average baseline ppFEV1 decline of 2.47% for adult patients receiving BSC in CUA 1 and 2.

CUA 3: F/RF

Despite having some residual CFTR function, patients with F/RF genotypes also have progressive decline in lung function over time, albeit at a slower rate than the F/F and F/MF populations. The baseline rate of ppFEV1 decline in patients treated with BSC alone in CUA 3 specific to the F/RF population is shown in Table 8. These values were derived from an analysis of the US CFF Patient Registry (years 2006 to 2014; (Sawicki et al, 2017)).

Pharmac staff met with CF clinicians in August 2021 who noted that generally the rate of decline in lung function for CF patients is 2-3% per year (Pharmac record on file - Minute

1.1.10). Hence, Pharmac consider the assumed baseline reduction for CF patients on BSC to be reasonable.

Long term reduction in lung function decline – ELX/TEZ/IVA

ELX/TEZ/IVA is assumed to reduce the annual decline in ppFEV1 by 90% for patients with a baseline ppFEV1 ≥70% and 65% for patients with a baseline ppFEV1 <70% in the base case and a range of 80% to 100% and 50% to 80% respectively, was tested in sensitivity analysis. In January 2022, Pharmac staff considered the clinical advice received from PTAC in November 2021 and the Respiratory Subcommittee in August 2021:

Respiratory Subcommittee – August 2021

3.30 The Subcommittee noted that further trials and longer term follow up studies are awaited to better quantify rate of lung function decline with time and the on-treatment clinical prognosis. However, the Subcommittee considered that the evidence indicating no on-treatment decline in ppFEV1 after 96 weeks despite an expected decline of 2-6% over this period from Study 105, with similar results observed in study 106, suggested it was highly likely that there would be a significant protective effect on long term lung function decline with ELX/TEZ/IVA.

PTAC - November 2021

10.23 The Committee noted that there is no long-term published data available past 24-weeks in patients over the age of 12, and that there is no published data for the use of ELX/TEZ/IVA in those under the age of 6 years. The Committee considered the strength and quality of evidence to be good overall but noted the lack of longer-term evidence and the variation between trial designs, specifically with regard to eligibility criteria and treatment run-in periods. The Committee considered that ppFEV1 is an important clinical outcome for these patients, and that 4-week studies are too short in duration to accurately measure any change. The Committee noted that there were few patients who discontinued ELX/TEZ/IVA due to adverse events, and that reported adherence rates were high for ELX/TEZ/IVA.

10.24 The Committee considered that there was uncertainty around the long-term consequences of using CFTR modulator therapies, and if CF patients will in fact experience near-normal lifespans. The Committee considered that it was unknown if incidence of CF-related comorbidities such CF-related diabetes or infertility would decrease. The Committee considered that there are no non-clinical features of the ELX/TEZ/IVA tablet that may impact on use, either by the patient, by family, or by healthcare workers, but noted that liquid formulations may need to be available if data emerges for efficacy in patients under the age of 6 years.

Subsequent to PTAC's November 2021 meeting, the Respiratory Specialist Advisory Committee (SAC) met in April 2022 and reaffirmed their consideration that ELX/TEZ/IVA would provide a significant protective effect on the lungs for people with CF (Respiratory SAC record 1.28, April 2022). The Respiratory SAC considered that patients with early-stage disease would be provided with a greater reduction in lung function decline than patients with established bronchiectasis and more advanced disease. At the April 2022 meeting, the Respiratory SAC provided Pharmac with estimates of the reduction in lung function decline from ELX/TEZ/IVA of 80% to 100% for patients with early-stage disease and 50% to 80% for late-stage disease patients (Respiratory SAC record 1.28, April 2022).

Pharmac staff note that the assumed reduction in long term lung function decline is a highly material parameter in the model, as it acts as the most significant surrogate for patient survival. Taking into account the advice from PTAC and the Respiratory Subcommittee Pharmac staff have implemented reduction in lung function decline in the CUA based on the midpoints in the ranges provided by the Respiratory SAC in April 2022. Pharmac staff have assumed a ppFEV1 of 70% to be a reasonable threshold to distinguish which patients at baseline may have early or late-stage disease and the associated reduction in lung function decline. This threshold is varied in sensitivity analysis and was not found to be impactful to the CUA result.

Table 8 – Summary of baseline age-dependent decline in ppFEV1 applied in the models.

Age group (years)	(F/F – CUA 1, F/M – CUA 2) Annual FEV_1 change	(F/RF – CUA 3) Annual FEV_1 change
6-8	-1.12%[a]	-0.80% [c]
9-12	-2.39%[a]	-0.80% [c]
13-17	-2.34%[a]	-0.57% [c]
18-25	-2.47%[b]	-1.85% [c]
25-100	-2.47%[b]	-1.06% [c]
Reduction in the rate of $ppFEV_1$ decline (all patients aged ≥6 years with baseline ppFEV1 ≥70%)	90.0% (ELX/TEZ/IVA) vs 0%(BSC)	90.0% (ELX/TEZ/IVA) vs 0%(BSC)
Reduction in the rate of $ppFEV_1$ decline (all patients aged ≥6 years with baseline ppFEV1 <70%)	65.0% (ELX/TEZ/IVA) vs 0%(BSC)	65.0% (ELX/TEZ/IVA) vs 0%(BSC)

Adapted with updates based on Pharmac current modelling, from: (Vertex Pharmaceuticals - Economic model report, 2021)
Sources:
[a] Konstan 2007
[b] de Boer 2011
[c] Sawicki *et al.* 2017

Weight-for-age-Z (WFAZ) score improvements

For patients treated with ELX/TEZ/IVA, the placebo-adjusted mean change from baseline in WFAZ is applied over the trial period. WFAZ was derived from the relevant clinical trials, and calculated for all patients assuming growth statistics of 20-year-olds for all patients aged >20 years.

Table 9 provides a summary of the model inputs for absolute change in WFAZ for ELX/TEZ/IVA, by age strata applied in CUA 1–3. After the initial change is applied, a patient's WFAZ is assumed to be constant for the remainder of the model simulation. Because treatment effects are placebo-adjusted, patients treated with BSC alone receive no acute increase and are assumed to have a constant WFAZ for the entire model time horizon.

Table 9 – Summary of inputs for increase in weight-for-age z-score (relative to BSC)

Age strata	Outcome/s	F/F		F/MF		F/RF	
		ELX/TEZ/IVA	BSC	ELX/TEZ/IVA	BSC	ELX/TEZ/IVA	BSC
6-11	Weight-for-age z-score (time)	+0.23 (24 weeks)	No change [a] (24 weeks)	+0.24 (24 weeks)	No change (24 weeks)	+0.24 (24 weeks)	No change (24 weeks)
12+		+0.41 (24 weeks)	No change [a] (24 weeks)	+0.30 (24 weeks)	No change (24 weeks)	+0.08 (8 weeks)	No change (8 weeks)

Sources: F/F: [Study 106, 109 & ITC Appendix]; F/MF: [Study 102, 106]; F/RF: [Study 106]. (Vertex Pharmaceuticals - Economic model report, 2021).

Reduction in pulmonary exacerbation (PEx)

The simulation model tracks PEx requiring treatment with intravenous (IV) antibiotics and/or hospitalisations. The occurrence of PEx is predicted contingent on patients' $ppFEV_1$ and age. The predictive equation is derived from the 2004 US CF Foundation Patient Registry, analysed by Goss et al 2007, who reported rates of PEx requiring treatment with IV antibiotics and/or hospitalisation to increase with lower $ppFEV_1$ (Goss et al, Exacerbations in cystic fibrosis. 1: Epidemiology and pathogenesis, 2007). The data reported were fitted to an exponential function, to model a continuous relationship between the PEx rates and ppFEV1, as outlined by the equation below (Whiting et al, 2014).

$$rate = ae^{-b \times ppFEV_1}$$

where rate is the annual rate of PEx and a and b are parameters defining the shape of the function. Two functions are estimated, including: one for patients aged 12–17 years (a=8.594, b=0.035), and another for patients aged 18+ years (a=3.789, b=0.026). The rate of exacerbations for BSC was not mutation-specific.

PEx rates for BSC are predicted conditional on ppFEV1 in each cycle over the model time horizon using the relationship above. The same approach is applied for CFTR modulators, using ppFEV1 simulated in the BSC arm of the CUA. To reflect the treatment benefit of CFTR modulators on PEx rates, the resulting rate is then multiplied by a PEx Rate Ratio.

Patients taking ELX/TEZ/IVA, in all CUAs, are assumed to experience the same reduction in PEx resulting in hospitalisation or IV antibiotics relative to BSC, as that observed in F/MF patients from Study 102 (RR: 0.22, 95% CI: 0.11 to 0.43; nominal P<0.0001) (Middleton et al, 2019). The PEx Rate Ratios corresponding to this study are shown in Table 10.

The Respiratory Subcommittee considered that, based on the evidence, it would be reasonable to assume that the 6 to 11-year-old age group would experience a similar reduction in PEx to that observed in the 12 years and older age group (3.48 of Respiratory Subcommittee record, August 2021). A similar reduction in the 6- to 11-year-old age group was explored in sensitivity analysis, but due to the relatively low rate of exacerbations in patients 6 to 11 years old, this assumption was immaterial to the CUA result when explored in sensitivity analyses Table 27.

Table 10 – Pulmonary exacerbation rate ratios (relative to BSC)

Age strata	Outcome/s	F/F		F/MF		F/RF	
		ELX/TEZ/IVA	BSC	ELX/TEZ/IVA	BSC	ELX/TEZ/IVA	BSC
6–11 years	Pulmonary exacerbation Rate Ratio	1	1.00[b]	1	1.00[b]	1	1.00[b]
12+ years		0.22	1.00[a]	0.22	1.00[a]	0.22	1.00[a]

Sources: Study 102

CF overall survival

Baseline mortality hazard

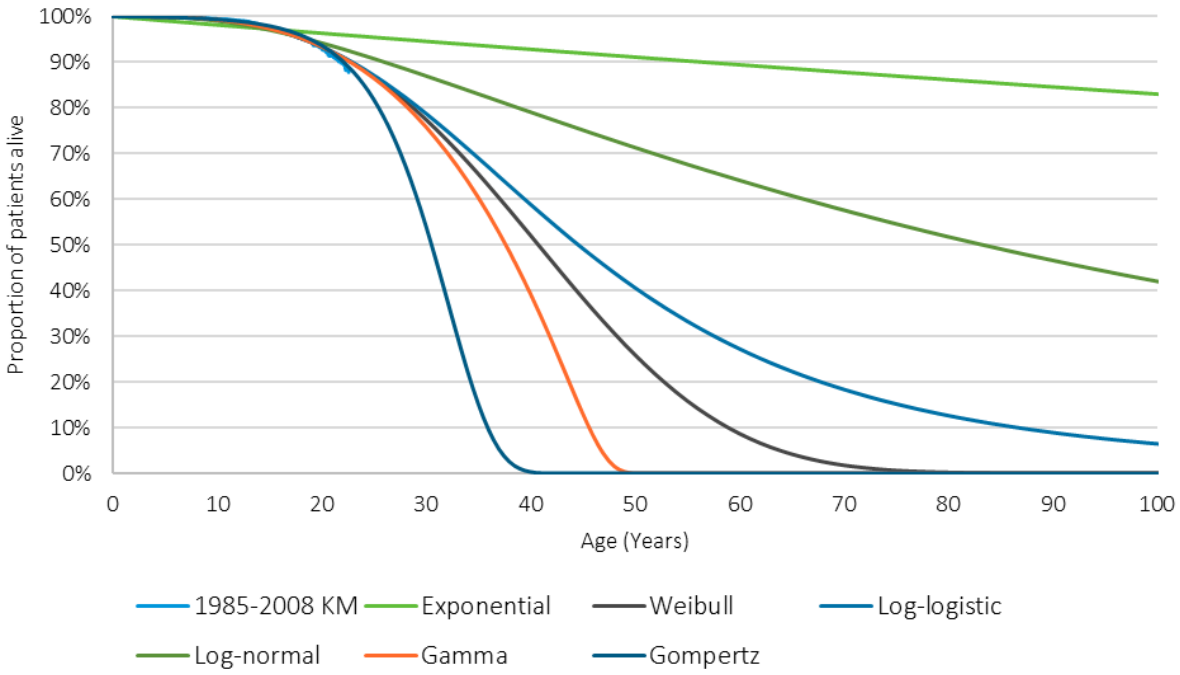
At the start of the simulation, individual patients are assigned a baseline hazard ratio representing their age-specific risk of mortality. In this analysis, survival curves from the UK CF data registry (birth cohorts 1985–2008) were used as a proxy to determine the baseline age-specific risk of mortality in NZ CF patients. A Weibull distribution (see Table 11 for parameters and Figure 2 for graph) was selected as having the best parametric fit (based on Akaike and Bayesian information criteria) and clinical plausibility, generating a median age of death for CF patients of 40.8 years. For further detail of the methodology used to calculate the baseline mortality in the model, see (Vertex Pharmaceuticals - Economic model report, 2021)

Table 11 – Parameters for Weibull distribution used to derive CF survival projections based on UK CF Registry population survival data (all genotypes, birth cohorts 1985-2008)

Description of the parameters of the Weibull function*	Parameter values
Scale (λ)	0.00000394
Shape (γ)	3.2577

*Weibull Survival Function: $S(t) = e^{-(\lambda t)^{\gamma}}$; Weibull Hazard Function: $h(t) = \lambda\gamma t^{\gamma-1}$

Figure 2 - Kaplan-Meier curve and parametric fits to the UK CF Registry population survival data (all genotypes, birth cohorts 1985-2008)



Annual adjustment of mortality hazard

After baseline, a patient's risk of mortality is re-calculated in each cycle of the model by adjusting for changes in clinical characteristics using the CPH model developed by Liou et al. (Liou et al, 2001). This model was based on data collected from 1993 to 1998 for the US CF Foundation Patient Registry, including 11,630 individuals aged 5.5 to 71.05 years. The following nine patient characteristics were found to predict survival: age, gender, ppFEV1, weight-for-age z-score, pancreatic sufficiency, diabetes, S. aureus infection, B. cepacia infection, and number of acute PEx per year (hazard rate coefficients outlined in Table 12 below). For further detail of the methodology in calculating the annual mortality hazard ratio which defined patients' risk of death in the model, see (Vertex Pharmaceuticals - Economic model report, 2021).

Pharmac staff note the approach to estimating CF patient survival is based on associations between clinical parameters and survival observed in the 1990s, and with long yet still limited follow up, relative to a patient's lifetime. Pharmac staff have considered the validity and uncertainty of the 2001 CPH survival model in light of this. The supplier provided commentary on this validity and uncertainty, as follows:

'While the CPH model has not been updated since its publication, the authors presented an updated validation in 2015 of the logistic regression that was originally published alongside the CPH model in 2001 (Liou & Adler, Five-year survivorship in cystic fibrosis: Outcomes improve, 2015)*. The updated logistic regression used US CFFPR data from 1993–2010. This analysis concluded that, while there were some slight changes to coefficients in the logistic regression model, the factors predicting mortality in patients with CF have remained stable.'*

The updated coefficients from Liou et al. in 2015 are outlined in Table 12 below. As the supplier alludes, Liou and peers re-evaluated the 5-year survival model using US CFFPR data from 1993-2016 and concluded that model coefficients estimated with the more recent follow up data were similar to previous estimates, showing that associations between demographic factors and survival remain largely unchanged (Liou, Kartsonaki, & Keogh, 2020). Further, Liou et al 2020 concluded that the original 5-year predicted survival model remains useful for stratifying individuals into expected survival groups for observational or

interventional studies of CF. Pharmac staff note, the methods used to predict survival in the supplier's economic model are extensively utilised in decision modelling for CFTR modulators and that the mean and median ages of death (39.7 and 38.7 years respectively) for CF patients treated with BSC in the model were broadly consistent with New Zealand estimates (PTAC record 10.13, November 2021). In addition, improvement in survival for patients treated with ELX/TEZ/IVA was tested across a range of values for long term lung function decline, and results appeared clinically plausible.

Table 12 – Cox proportional hazards model of cystic fibrosis

Covariate	Coefficient (2001)	Coefficient (2015)
Age	0.011	0.016
$ppFEV_1$	-0.042	-0.046
Sex	0.15	0.27
Weight-for-age z-score	-0.28	-0.276
Pancreatic sufficiency	-0.14	-0.275
Diabetes mellitus	0.44	0.496
S. aureus	-0.25	-0.193
B. cepacia	1.41	1.085
Annual number of acute exacerbations (max 5)	0.35	0.399
Exacerbations × *B. csepacia*	-0.28	-0.28

Other model inputs

A summary of the remaining input parameters applied in the ELX/TEZ/IVA economic analyses are presented in Table 13. The table presents the rates of treatment discontinuation, adverse events (AEs), and lung transplantation, and post lung transplant mortality. These parameters are overall not material to the analysis and full commentary on how they were derived can be found in the supplier's economic modelling report (Vertex Pharmaceuticals - Economic model report, 2021).

Table 13 – Other inputs to the economic model

Input parameter	CUA 1 (F/F)		CUA 2 (F/MF) CUA 2 (F/MF)		CUA 3 (F/RF)		Source
	ELX/TEZ/IVA	BSC	ELX/TEZ/IVA	BSC	ELX/TEZ/IVA	BSC	
Discontinuation							
6–11 years of age: Annual rate of discontinuation during trial period	0.067	NA	0.067	NA	0.067	NA	CUA 1–3: [ELX/TEZ/IVA Study 106]
≥12 years of age: Annual rate of discontinuation during trial period	0.025	NA	0.033	NA	0.049	NA	CUA 1: [ELX/TEZ/IVA Study 109] CUA 2: [ELX/TEZ/IVA Study 102] CUA 3: [ELX/TEZ/IVA Study 104]
Annual rate of discontinuation beyond trial period	0.00	0.00	0.00	0.00	0.00	0.00	Assumption.
AE annual incidence 6–11 years of age							
Headache	0.602	0.202	0.602	0.202	0.602	0.202	CUA 1: [ELX/TEZ/IVA Study 106; BSC Study 109] CUA 2: [ELX/TEZ/IVA Study 106; BSC Study 109] CUA 3: [ELX/TEZ/IVA Study 106; BSC Study 109]
Upper respiratory tract infection	0.395	0.226	0.395	0.226	0.395	0.226	
Abdominal pain	0.280	0.226	0.280	0.226	0.280	0.226	
Diarrhoea	0.243	0.088	0.243	0.088	0.243	0.088	
Rash	0.280	0.022	0.280	0.022	0.280	0.022	
Alanine aminotransferase increased	0.243	0.202	0.243	0.202	0.243	0.202	
Nasal congestion	0.356	0.179	0.356	0.179	0.356	0.179	
Blood creatine phosphokinase increased	0.067	0.000	0.067	0.000	0.067	0.000	
Aspartate aminotransferase increased	0.067	0.156	0.067	0.156	0.067	0.156	
Rhinorrhea	0.280	0.110	0.280	0.110	0.280	0.110	
Rhinitis	0.000	0.110	0.000	0.110	0.000	0.110	
Influenza	0.243	0.133	0.243	0.133	0.243	0.133	
Sinusitis	0.033	0.088	0.033	0.088	0.033	0.088	
Blood bilirubin increased	0.033	0.000	0.033	0.000	0.033	0.000	
AE annual incidence ≥12 years of age							
Headache	0.734	0.350	0.412	0.350	0.566	0.350	

Input parameter	CUA 1 (F/F)		CUA 2 (F/MF) CUA 2 (F/MF)		CUA 3 (F/RF)		Source
	ELX/TEZ/IVA	BSC	ELX/TEZ/IVA	BSC	ELX/TEZ/IVA	BSC	
Upper respiratory tract infection	0.237	0.288	0.374	0.288	0.099	0.288	CUA 1: [ELX/TEZ/IVA Study 109; BSC Study 102] CUA 2: [ELX/TEZ/IVA & BSC Study 102] CUA 3: [ELX/TEZ/IVA Study 104; BSC Study 102]
Abdominal pain	0.102	0.203	0.336	0.203	0.354	0.203	
Diarrhoea	0.209	0.156	0.299	0.156	0.251	0.156	
Rash	0.182	0.111	0.238	0.111	0.099	0.111	
Alanine aminotransferase increased	0.155	0.077	0.226	0.077	0.406	0.077	
Nasal congestion	0.155	0.168	0.214	0.168	0.200	0.168	
Blood creatine phosphokinase increased	0.102	0.099	0.214	0.099	0.099	0.099	
Aspartate aminotransferase increased	0.128	0.044	0.214	0.044	0.406	0.044	
Rhinorrhea	0.076	0.066	0.190	0.066	0.149	0.066	
Rhinitis	0.102	0.122	0.167	0.122	0.000	0.122	
Influenza	0.076	0.033	0.156	0.033	0.099	0.033	
Sinusitis	0.050	0.088	0.121	0.088	0.000	0.088	
Blood bilirubin increased	0.025	0.022	0.110	0.022	0.200	0.022	
Lung transplantation							
$ppFEV_1$ threshold for lung transplant eligibility ($ppFEV_1$)	30%	30%	30%	30%	30%	30%	(Bell et al, 2008)
Proportion of eligible patients that receive transplant	12.1%	12.1 %	12.1%	12.1 %	12.1%	12.1 %	Calculated: Average percentage of patients ≥12 years of age with severe lung impairment receiving a bilateral lung transplant NZCFDR 2011-2016.
Annual probability of death first year post-transplant	13.5%	13.5 %	13.5%	13.5 %	13.5%	13.5 %	NZ Lung transplants CF March 93–DEC 2019 CF (O'Carroll 2021) Objective link - 2.3.2 DHB

Input parameter	CUA 1 (F/F)		CUA 2 (F/MF) CUA 2 (F/MF)		CUA 3 (F/RF)		Source
	ELX/TEZ/IVA	BSC	ELX/TEZ/IVA	BSC	ELX/TEZ/IVA	BSC	
							Stakeholder meeting lung transplant in New Zealand
Annual Probability of Death Subsequent Years Post-Transplant	4.1%	4.1%	4.1%	4.1%	4.1%	4.1%	NZ Lung transplants CF March 93–DEC 2019 CF (O'Carroll 2021) Objective link - 2.3.2 DHB Stakeholder meeting lung transplant in New Zealand

As adapted from (Vertex Pharmaceuticals - Economic model report, 2021).

4.4 Health-Related Quality of Life

HRQoL utility weights

Base case utility estimates

HRQOL utility weights used by Pharmac in the base case are sourced from an economic evaluation of CF treatments, outlined in Table 14 (Schechter et al, 2015). Schechter et al reported health utility weight estimates in Euro-QoL 5-dimensions (EQ-5D) based on ppFEV_1 in patients with CF as follows: FEV_1 > 70% predicted, EQ-5D = 0.864; FEV_1 40–69% predicted, EQ-5D = 0.810; FEV_1 < 40% predicted, EQ-5D = 0.641. Linear interpolation from these estimates was used to predict EQ-5D scores in the FEV1-defined health states outlined in Table 14 below.

These values were elicited via patient-report, though derived using the Cystic Fibrosis Questionnaire Revised (CFQ-R) and mapped to the EQ-5D (methods detailed by Bradley et al and further reported in economic analysis by Tappenden et al) (Bradley et al, 2013) (Tappenden et al, 2014). A high level of consistency was reported between CFQ-R and EQ-5D utility weights obtained in this study.

When selecting appropriate HRQoL utility weights, the Prescription for Pharmacoeconomic Analysis (2015) recommends that the New Zealand EQ-5D Tariff 2 should be referred to first, and should be used preferentially to describe the health states. The Global Burden of Disease disability weights and published literature are recommended to validate these values, to check for consistency with the estimated EQ-5D values.

EQ-5D 3L weights were not supplied or generated for this proposal. Norman et al (2018) undertook a review of seven country-specific EQ-5D-5L value sets, and identified striking similarities in western countries (Canada, England, Netherlands and Spain) in terms of : (a) the relative importance of the 5 dimensions; (b) the relative utility decrements across the five levels; and (c) the scale length.

The EQ-5D weights reported by Schechter et al. were obtained in the United Kingdom, and therefore, would be expected to be reasonably comparable to utility weights obtained using the New Zealand EQ-5D Tariff 2, were these available. Given this and the information above, Pharmac considered the utility values provided by Schechter et al to be most reasonable to inform base case health state utility weights.

Pharmac staff subject the HRQoL values to sensitivity analysis below to test the materiality of the source of utility weights in each disease state to the CUA result.

Table 14 – Utility estimates across ppFEV and lung transplant health states reported by Schechter et al.

ppFEV1 (%)	*Utility*
>90	0.920
80-89	0.873
70-79	0.838
60-69	0.801
50-59	0.765
40-49	0.729
30-39	0.692
20-29	0.653
<20	0.625
Pre-lung transplant	0.310*

**Sourced from* (Anyanwu et al, 2002).

From the utilities reported by Schechter et al, Pharmac staff calculated an average health utility weight for normal ($ppFEV_1$ > 90%), mild ($ppFEV_1$ 70-90%), moderate ($ppFEV_1$ 40-70%) and severe ($ppFEV_1$ <40%) health states outlined in Table 15. For example, for the severe health state of 0.570, this value is informed by an average of 0.692, 0.653, 0.625 and 0.310. The pre-lung transplant utility used in the CUA was sourced from Anyanwu et al. as no such value was available in the Schechter study (Anyanwu et al, 2002). The health utility weights for pre-lung transplantation are informed by an economic evaluation of lung transplantation along with post-lung transplant health utility weights outlined in Table 17 (Anyanwu et al, 2002).

Table 15 – Base case health utility weights

Clinical characteristics	Mean health utility weight (BSC)	Mean health utility weight (ELX/TEZ/IVA)	Source
Normal ($ppFEV_1$ >90%)	0.92	0.999	Schechter et al,2015
Mild ($ppFEV_1$ 70-90% predicted)	0.856	0.935	Schechter et al,2015
Moderate ($ppFEV_1$ 40-70% predicted)	0.765	0.844	Schechter et al,2015
Severe ($ppFEV_1$ <40% predicted)	0.570	0.649	Schechter et al,2015
Treatment-specific utility increment	-	0.079	Supplier estimate

Utilities provided by the supplier

The Supplier has estimated the mean health utility weight for each group based on lung function, as outlined in Table 16 below. The CF health state utility estimates provided were based on responses to an EQ-5D survey sent to 25 CF clinicians in Australia, of whom ten responded within the available ten days. Of these, seven completed the EQ-5D-5L questions by proxy. The survey contained EQ-5D-5L questions relating to four health profiles representing four CF health states of differing severity: >90% predicted FEV1 (normal), 70-

90% predicted FEV1 (mild), 40-70% predicted FEV1 (moderate), <40% predicted FEV1 (severe). EQ-5D-5L utility weights were generated using the UK valuation set, using the recommended crosswalk from EQ-5D-3L, (van Hout B, 2012) outlined in Table 16. Pharmac staff noted in August 2021 that the supplier estimates were limited by small sample size and research that shows that proxy-reported HRQOL tended to be lower than self-reported HRQoL (Rand et al, 2015). Due to the small sample size and the limitations in the methodology, Pharmac considered the supplier health utility weight estimates to be reasonable to test in sensitivity analysis, not in the base case.

Table 16 – Supplier health utility weight estimates

Clinical characteristics	Mean health utility weight (BSC)	Mean health utility weight (ELX/TEZ/IVA)	Source
Normal ($ppFEV_1$ >90%)	0.98	1	CF clinician EQ-5D survey
Mild ($ppFEV_1$ 70-90% predicted)	0.88	0.96	CF clinician EQ-5D survey
Moderate ($ppFEV_1$ 40-70% predicted)	0.67	0.75	CF clinician EQ-5D survey
Severe ($ppFEV_1$ <40% predicted)	0.37	0.45	CF clinician EQ-5D survey
Treatment-specific utility increment	-	0.079	Supplier estimate

Alternative health utility weight estimate provided by the supplier

Noting the issues with the sample size of the clinician survey health utility weight estimates, the supplier provided EQ-5D utility values derived from the STRIVE trial (Ramsey et al, 2011). The supplier recommended that utilities based on the regression equation below be applied to the economic model in sensitivity analyses. The equation was developed using ppFEV1 and PEx data collected from all 161 patients in STRIVE over 48 weeks (Solem et al, 2016). These patients contributed a total of 1,214 sets of observations. 72 (44.7 % of total 161) patients experienced any PEx. 146 PEx were observed overall, including 52 (35.6 %) that required hospitalisation (Solem et al, 2016). Mixed-effects models with repeated measures were employed to describe the association of PEx and ppFEV1 with EQ-5D measures (Solem et al, 2016).

The following relationship was derived between EQ-5D utility scores, ppFEV1, and PEx requiring treatment with IV antibiotics and/or hospitalisation:

Regression equation deriving the relationship between EQ-5D, FEV1 and PEx.

$$U = 0.686 + 0.535 \times ppFEV_1 + -0.274 \times ppFEV_1{}^2 \quad 0.07 \times PEx\ (Hospitalisation)$$

Treatment-specific utility improvement

The supplier has estimated a treatment-specific utility increment for patients treated with ELX/TEZ/IVA, based on improvements across multiple non-respiratory domains of the CFQ-R in studies 102 and 103 and mapping these to the EQ-5D using an algorithm developed by Acaster et al (Acaster et al, 2015). The Respiratory Subcommittee (Respiratory Subcommittee record 3.52) considered that estimates of health utility weight correlating to clinical ppFEV1 and improvement in ppFEV1 are respiratory disease-specific and may not capture the full multidimensional impact of cystic fibrosis on HRQoL. Pharmac staff considered in August 2021, the utility increment provided by the supplier appeared reasonable and captures improvements in HRQOL associated with non-respiratory dimensions for patients treated with ELX/TEZ/IVA.

Additional utilities

The economic model also captures health utility weight for patients who have undergone lung transplantation and disutility associated with pulmonary exacerbation events over an average duration of 14 days (Goss et al, Acute pulmonary exacerbation in cystic fibrosis, 2019) (Anyanwu et al, 2002) (Sharma et al, 2018).

Table 17 – Additional utilities captured in the model

Clinical characteristics	Mean health utility weight (BSC)	Mean health utility weight (ELX/TEZ/IVA)	Source
Post-transplant utility (year 1)	0.79	0.79	(Anyanwu et al, 2002)
Post-transplant utility (year 2)	0.82	0.82	(Anyanwu et al, 2002)
Post-transplant utility (year 3)	0.815	0.815	(Anyanwu et al, 2002)
Post-transplant utility (year 4+)	0.82	0.82	(Anyanwu et al, 2002)
Pulmonary exacerbation disutility	-0.17	-0.17	(Sharma et al, 2018)

4.5 Costs

4.5.1 Pharmaceutical Cost

ELX/TEZ/IVA

The cost of ELX/TEZ/IVA is outlined in Table 18 below. ELX/TEZ/IVA is taken twice daily at a recommended daily dosage of 200mg ELX, 100mg TEZ and 150mg IVA in the morning and 150mg IVA in the evening for patients over 30kg and 100mg ELX, 50mg TEZ and 75mg IVA in the morning and 75mg IVA in the evening for patients under 30kg. The average annual cost per patient of ELX/TEZ/IVA is estimated to be [redacted], which assumes an average adherence rate of 95% (see below).

Adherence

The supplier's submission assumed an average adherence rate of 90%. The Respiratory Subcommittee noted an American study that reported treatment adherence to IVA and LUM/IVA to be 84%, and adherence to TEZ/IVA to be 92% (Mehta et al, 2021). The Subcommittee considered that given the efficacy of ELX/TEZ/IVA, adherence to this treatment is likely to be greater than 92% if it were funded in New Zealand (Respiratory Subcommittee record 3.50, August 2021). Pharmac staff agreed that a 95% adherence rate was reasonable in the base case and 90% to 100% adherence should be tested in sensitivity analysis.

Table 18 – ELX/TEZ/IVA pharmaceutical Cost

Description	ELX/TEZ/IVA
List price per annum	[redacted]
List price per 28-day pack	[redacted]
Effective price per annum (100% compliance)	[redacted]
Effective price per annum (95% compliance)	[redacted]
Effective price per 28-day pack	[redacted]

(Vertex Pharmaceuticals - Economic model report, 2021)

Pharmaceutical cost after patent expiry

The net pharmaceutical cost in the model is assumed in the base case to reduce by [redacted] years from date of listing. Date of listing and the model start date are assumed to be the same, at August 2022. This is based on the patent expiry on the [redacted], and an assumed price reduction one year after loss of exclusivity (LoE), as outlined in Table 19 below. This assumption is consistent with the previous Ivakaftor submission and with the guidance outlined in Pharmac's PFPA v2.2. This assumption is varied in sensitivity analysis.

Table 19 – Patent expiry assumptions

Item	Value	Description
Time from model start to LoE (Years)	[redacted]	Sponsor estimate
% Price Reduction 1 Year After Loss of Exclusivity	[redacted]	Assumption. Consistent with previous IVA submission
Net Pharmaceutical price per pack After Loss of Exclusivity	[redacted]	Calculation

BSC pharmaceutical cost

BSC pharmaceutical cost has been estimated based on an Australian cost of illness study which reported medicine usage by disease severity (van Gool et al, 2013). Treatments outlined in Van Gool et al. include: acute and chronic antibiotic therapy, nutritional supplementation, mucolytics, inhaled bronchodilators and steroidal anti-inflammatories, each of which were costed using net pharmaceutical pricing in New Zealand. The proportion of patients on each treatment, in each disease severity subgroup was used to calculate an average BSC pharmaceutical cost for normal/mild, moderate and severe CF health states, outlined in Table 20 below.

BSC pharmaceutical cost on ELX/TEZ/IVA

BSC pharmaceutical costs for patients treated with ELX/TEZ/IVA have been assumed to decrease with a reduced requirement for oral nutritional supplements, acute and chronic antibiotics, and mucolytic agents such as, dornase alfa and hypertonic saline. The supplier's economic analysis assumed no change in BSC pharmaceutical cost, due to the core trials requiring patients to continue on BSC therapy, whether treated with ELX/TEZ/IVA or comparator interventions.

However, the Respiratory Subcommittee in August 2021 considered over time there would be an 80% reduction in the use of BSC, including a substantial reduction in antibiotic use, hypertonic saline and dornase alfa (Respiratory Subcommittee record 3.54, August 2021). Further, consultation with physicians treating people with considered the need for dietary supplementation would reduce significantly. Pharmac staff consider it reasonable consequently to reduce the cost associated with antibiotic, mucolytic and nutritional supplements by 80% in the base case, and by 50% to 100% in sensitivity analysis. In the base case, this is equivalent to a 43% to 55% reduction in the total BSC pharmaceutical costs (including other pharmaceuticals expected to be used at the same rate across treatment arms) for patients treated with ELX/TEZ/IVA, outlined in Table 20 below.

Table 20 – Average annual pharmaceutical cost by CF disease severity

Item	Normal/mild (≥70% FEV)	Moderate (40%to 70% FEV)	Severe (<40%)
Annual BSC pharmaceutical cost (BSC)	[redacted]	[redacted]	[redacted]
Annual BSC pharmaceutical cost (ELX/TEZ/IVA)	[redacted]	[redacted]	[redacted]

For full calculations see – Trikafta supportive calculations

4.5.3 Health Sector Costs

In addition to pharmaceutical costs, Van Gool et al. also reported medical service costs and inpatient health service usage by disease severity.

Medical services

Medical services which Van Gool et al report being used by people with CF include: pathology, lung function and sweat chloride testing, regular clinic visits, CFTR genotyping, oxygen therapy and CF-related procedures. The annual units and costs of each medical service, stratified by disease severity are outlined in Table 21 below.

Table 21 – Medical service costs

Item	Source	NZ unit cost estimate	Annual units - normal/mild ≥70% FEV	Cost - normal/mild ≥70% FEV	Annual units - moderate 40%-70% FEV	Cost - moderate 40%-70% FEV	Annual units - severe <40% FEV	Cost - severe <40%
Pathology tests – microbiology sputum, full blood count, liver function, vitamin A, D, E levels, oral glucose tolerance and faecal fat.	Cost spreadsheet	$324	2.7	$820	4.7	$1,428	6.0	$1,823
Lung function	Cost spreadsheet	$322	1.7	$547	3.7	$1,191	3.1	$998
Clinical visits (Initial each year)	Cost spreadsheet	$736	1	$736	1	$736	1	$736
Clinical visits (subsequent)	Cost spreadsheet	$510	3.6	$1,834	4.9	$2,497	5.1	$2,598
Endoscopy	Cost spreadsheet - DRG K40A, B, C weighted average	$4,665	0.022	$87.8	0.037	$148	0.061	$243
Therapeutic bronchial artery embolization	Cost spreadsheet - weighted average E61A, B	$7,322	0.001	$6	0.013	$81	0.017	$106
Sweat chloride test	Cost spreadsheet	$32	0.015	$0	0.001	$0	0	$0
CFTR mutation analysis	Cost spreadsheet	$267	0.021	$6	0.006	$2	0.008	$2
Oxygen therapy	Cost spreadsheet	$614	0.001	$1	0.016	$10	0.135	$83
Total cost			**Normal/ mild ≥70% FEV**	**$4,110**	**Moderate 40%-70% FEV**	**$6,237**	**Severe <40% FEV**	**$6,855**

For full calculations see – Trikafta supportive calculations

Inpatient costs

Inpatient costs outlined by Van Gool et al. include the average annual hospital days and hospital events stratified by disease severity. The average annual hospital days and events were used to inform an average length of stay per PEx event for each CF health state. A weighted average daily cost of $1,764 is applied, informed by inpatient cost data for CF-specific DRG codes E60A and E60B. Estimated average inpatient PEx event costs are outlined in Table 22 below.

Home IV

Rates of home IV outlined by Van Gool et al are included in the average cost of a PEx event. Intravenous antibiotics are typically initiated in hospital and continued at home if deemed appropriate by treating clinicians and desired by patients. Pharmac has assumed that for patients undertaking home IV antibiotics, initial inpatient costs are captured in the average inpatient event cost but incur an additional cost for home IV antibiotics. A comprehensive breakdown of the New Zealand relevant cost of home IV antibiotic therapy could not be identified, however Pharmac staff have estimated the cost of home IV therapy by costing key components of home IV therapy, including nurse and hospital pharmacist time, antibiotic costs and monitoring costs over an average duration of 10 days. The total cost of home IV therapy for 10 days has been estimated to be $1,898 ($189.8 per day).

Table 22 – Inpatient pulmonary exacerbation costs

Item	Normal/mild ≥70% FEV1	Moderate 40%-70% FEV1	Severe <40% FEV1
Hospital days	6.1	17.4	24.5
Hospital events	0.9	1.7	2.2
Hospital days per event	6.8	10.24	11.14
Inpatient cost per exacerbation event	**$11,961**	**$18,063**	**$19,653**
Home IV antibiotics rate	0.088	0.256	0.337
Home IV cost ($1,898)	$167	$486	$639
Total PEx event cost	**$12,128**	**$18,549**	**$20,293**

Pharmac staff note the health sector cost data reported by the Auckland DHB in response to an Official Information Act (OIA) request in 2021 (Auckland DHB, 2021). The OIA response outlined average annual health sector costs for CF patients aged 0 to 40 years, ranging from $7,638 (for people in the 1-4 year age group) to $52,176 (for people in the 20-24 age group) per year. Pharmac staff consider the estimates provided by the Auckland DHB to be useful but cannot be validated and are limited in their use for the purpose of economic modelling as the estimates are not provided by disease severity and not consistent with CF health states captured in the economic model. Pharmac staff considers the estimates for inpatient and medical service costs outlined in Table 21 and Table 22 above to be reasonably in line with the costs reported by the Auckland DHB. For example, a CF patient in a mild/normal or a severe health state in the economic model experiencing 1-2 PEx annually would incur health sector costs of $16,100 to $28,200 and $26,900 to $47,200 respectively, which is broadly consistent with the annual health sector costs outlined by the Auckland DHB.

Lung transplantation cost
The cost of a lung transplant was informed by an OIA request of the Auckland District Health Board (Auckland DHB, 2021). The OIA response reported the average cost of a lung transplant to be $287,958.

4.6 Cost-Effectiveness Results

Cost effectiveness results presented are based on a weighted average of the CUA results for each of the three genotype subgroups – F/F (59.1%) F/MF (25.4%) and F/RF (15.5%).

Eligible CF patients aged 6 years and over
The incremental cost is estimated to be [redacted], with a QALY gain of 9.28. The estimated cost-utility in QALYs per $1million is therefore [redacted] (cost per QALY of [redacted]). This is shown in Table 23 below, and the cost implications split by cost type are shown in Table 24.

Table 23 – Cost-Effectiveness Results for eligible people with CF aged 6 years and over

	ELX/TEZ/IVA	BSC	Incremental
QALYs	18.11	8.83	9.28
Cost	[redacted]	[redacted]	[redacted]
QALYs per $1m			[redacted]

Costs and QALYs discounted by 3.5%

Table 24 – Cost Implications to the Pharmaceutical Schedule, DHBs, and Patients for patients aged 6 years and over

	ELX/TEAZ/IVA	BSC	Incremental
Intervention cost to Pharmaceutical Schedule	[redacted]	$0	[redacted]
Medical service and BSC pharmaceutical costs	$181,454	$176,928	$4,526
PEx-Related costs	$57,488	$274,235	-$216,747
Lung Transplant costs	$3,540	$20,849	-$17,308
Adverse event costs	$4,632	$2,693	$1,940
Monitoring cost	$1,794	$0	$1,794
TOTAL COSTS	[redacted]	$474,704	[redacted]

Costs discounted by 3.5%

Eligible patients 12 years and over
The incremental cost is estimated to be [redacted] with a QALY gain of 8.74. The estimated cost utility, in QALYs per $1million, is therefore [redacted] (cost per QALY of [redacted]). This is shown in Table 25 below, and the cost implications split by cost type are shown in Table 26.

Table 25 – Cost-Effectiveness Results for eligible people with CF aged 12 years and over

	ELX/TEZ/IVA	BSC	Incremental
QALYs	16.24	7.50	8.74
Cost	[redacted]	[redacted]	[redacted]
QALYs per $1m			[redacted]

Costs and QALYs discounted by 3.5%

Table 26 – Cost Implications to the Pharmaceutical Schedule, DHBs, and Patients for patients aged 12 years and over

	ELX/TEZ/IVA	BSC	Incremental
Intervention cost to Pharmaceutical Schedule	[redacted]	$0	[redacted]
Medical service and BSC pharmaceutical costs	$174,317	$159,473	$14,844
PEx-Related costs	$59,470	$261,887	-$202,417
Lung Transplant costs	$4,266	$23,593	-$19,328
Adverse event costs	$4,246	$2,171	$2,075
Monitoring cost	$1,668	$0	$1,668
TOTAL COSTS	[redacted]	$447,124	[redacted]

Costs discounted by 3.5%

The cost-offsets in the model are primarily due to reduced health sector costs associated with reduced PEx for patients who receive ELX/TEZ/IVA. Due to increased survival of patients treated with ELX/TEZ/IVA however, additional cost is incurred in the intervention arm of the model from ongoing medical, BSC pharmaceutical and PEx costs. Despite the considerable expense of lung transplantation, overall lung transplantation rates in the model are low and represent a modest saving from treatment.

Ultimately, the high pharmaceutical cost of ELX/TEZ/IVA treatment over the patient's lifetime drives the CUA result in QALYs per $ million down, in spite of these cost offsets and the high incremental benefit of ELX/TEZ/IVA relative to BSC in QALYs gained.

4.7 Sensitivity Analysis

Table 27 – Sensitivity Analysis CF patients 6 years and over

Input	Base-Case Value	Low Value	High Value	Range QALYs per $m
Base Case	-	-	-	[redacted]
Threshold for advanced stage disease	70%	60%	80%	[redacted]
Reduction in long term lung function decline - ppFEV1 ≥70% / ppFEV1 <70%	90%/65%	80%/50%	100%/80%	[redacted]
Utilities (Clinician proxy utilities)	-			[redacted]
Utilities (Regression equation)	-			[redacted]
Utilities (removal of treatment specific utility increment)	0.079	0	0.079	[redacted]
Exacerbation costs (% of base case)	100%	50%	150%	[redacted]
Mucolytic, hypertonic saline, antibiotic and nutritional supplement pharmaceutical cost reduction with ELX/TEZ/IVA	80%	0%	100%	[redacted]
Adherence rate	95%	90%	100%	[redacted]
Exacerbation rate reduction in 6–11-year-old CF patients as in 12+ group	1	-	0.22	[redacted]
Exacerbation rate reduction (12 years and over)	0.22	0.11	0.42	[redacted]
Cost of lung transplant	$287,958	$158,153	$872,336	[redacted]
Time horizon	Lifetime	20 years	Lifetime	[redacted]

Price reduction at patent expiry	[redacted]	[redacted]	[redacted]	[redacted]
Baseline survival function (5 years above and below median)	40.1 years	35.8 years	45.8 years	[redacted]

Table 28 – Sensitivity Analysis CF patients 12 years and over

Input	Base-Case Value	Low Value	High Value	Range QALYs per $m
Base Case	-	-	-	[redacted]
ppFEV1 threshold for advanced stage disease	70%	60%	80%	[redacted]
Reduction in long term lung function decline - ppFEV1 ≥70% / ppFEV1 <70%	90%/65%	80%/50%	100%/80%	[redacted]
Utilities (Clinician proxy utilities)	-			[redacted]
Utilities (Regression equation)	-			[redacted]
Utilities (removal of treatment specific utility increment)	0.079	0	0.079	[redacted]
Exacerbation costs (% of base case)	100%	50%	150%	[redacted]
Mucolytic, antibiotic and nutritional supplement pharmaceutical cost reduction with ELX/TEZ/IVA	80%	0%	100%	[redacted]
Adherence rate	95%	90%	100%	[redacted]
Exacerbation rate reduction (12 years and over)	0.22	0.11	0.42	[redacted]
Cost of lung transplant	$287,958	$158,153	$872,336	[redacted]
Time horizon	Lifetime	20 years	Lifetime	[redacted]
Price reduction at patent expiry	[redacted]	[redacted]	[redacted]	[redacted]
Baseline survival function	40.1 years	35.8 years	45.8 years	[redacted]

Parameters with higher sensitivity

The CUA result is most sensitive to the reduction in the long-term reduction in lung function decline for patients treated with ELX/TEZ/IVA, pharmaceutical cost, the treatment-associated utility increment from ELX/TEZ/IVA and model time horizon. The reduction in long term lung function decline from ELX/TEZ/IVA is influential in reducing the rate at which patients transition to severe CF health states and as a surrogate for overall survival in the model. This parameter has significant uncertainty with currently only 96 weeks of interim data available for ELX/TEZ/IVA from Study 105, to inform long term outcomes. The CUA result is sensitive to the removal of a net price reduction at the time of patent expiry ([redacted] into the model) and reduction in the assumed price reduction from [redacted], due to the high treatment cost of ELX/TEZ/IVA. The CUA result is sensitive to reducing the time horizon from lifetime in the base case to 20 years, as a shorter time horizon does not capture the long-term survival benefits assumed to be associated with ELX/TEZ/IVA treatment.

Parameters with lower sensitivity

The CUA result is least sensitive to different health state utilities, the ppFEV1 threshold for advanced stage disease, inpatient exacerbation costs, BSC pharmaceutical cost reduction with ELX/TEZ/IVA treatment, treatment adherence rate, exacerbation rate reduction with ELX/TEZ/IVA and lung transplant costs.

4.8 Summary of Overall Cost-Effectiveness

Eligible CF patients 6 years and over
As outlined above, the base-case cost utility estimate is [redacted]. Taking into account the results of the sensitivity analysis, the highly likely range is estimated to be [redacted]. This range captures uncertainty in the long-term reduction in lung function decline as a result of ELX/TEZ/IVA treatment and dynamic pricing of ELX/TEZ/IVA (price changes at patent expiry). The range is extremely narrow and insensitive to changes to most parameters, due to the very high treatment cost of this medicine, with minimal health sector cost offsets.

Eligible CF patients 12 years and over
As outlined above, the base-case cost utility estimate is [redacted]. Taking into account the results of the sensitivity analysis, the highly likely range is estimated to be [redacted]. This range captures uncertainty in the long-term reduction in lung function decline as a result of ELX/TEZ/IVA treatment and dynamic pricing of ELX/TEZ/IVA. The range is extremely narrow and insensitive to changes to most parameters, due to the very high treatment cost of this medicine, with minimal health sector cost offsets.

5. Budget Impact Analysis

5.1 Summary of Budget Impact

Eligible CF patients 6 years and over

The 5-year net present value (NPV) to the hospital Pharmaceutical Schedule of funding ELX/TEZ/IVA is estimated to be [redacted] with a cost in the first 12 months of [redacted] The 5-year NPV to DHBs is estimated to be [redacted] All costs are discounted at a rate of 8%.

Eligible CF patients 12 years and over

The 5-year NPV to the hospital Pharmaceutical Schedule of funding ELX/TEZ/IVA is estimated to be [redacted] with a cost in the first 12 months of [redacted] The 5-year NPV to DHBs is estimated to be [redacted] All costs are discounted at a rate of 8%.

The budget impact takes into account:

- patient numbers estimated from CF port epidemiological data available for 2020 and extrapolating prevalent patient number growth to 2022
- pharmaceutical cost of patients taking ELX/TEZ/IVA, assuming a 95% adherence rate and utilising relevant trial discontinuation rates during the first year on treatment
- pharmaceutical savings resulting from decreased usage of hypertonic saline, dornase alfa, continuous tobramycin and ivacaftor
- health sector savings from reduced PEx resulting in hospitalisation and reduced lung transplantation

5.2 Patient Numbers

The total number of CF patients in New Zealand in 2022 is estimated to be 510, calculated by averaging the annual growth in CF prevalence from 2012 to 2020 (1.9%) and applying this annually to the number of CF patients reported in 2020 (491) up to 2022 (510) (Port CF Data Registry, 2020).

Of all CF patients, 81% are estimated to be 6 years and older and 64% to be 12 years and older and 87.6% of patients are assumed to have at least one F mutation in the CFTR gene (Port CF Data Registry, 2020).These estimates are outlined in Table 29 below.

Table 29 – F/any patient population in New Zealand by age and genotype subpopulation

Genotype	Number of patients	Proportion of patients
Total patients	**491**	**-**
Patients aged 6 years and over	**396**	**80.7%**
Patients aged 12 years and over	**314**	**64.0%**
Genotyped patients	**488**	**-**
Patients with at least one *F508del-CFTR* mutation	**430**	**87.6%**
F/F[#]	**241**	**56.0%**
F/RF[#]	**29**	**6.7%**
F/G[#]	**22**	**5.1%**
F/MF[#]	**82**	**19.1%**
F/R117H[#]	**21**	**4.9%**
F/not yet characterised[#]	**35**	**8.1%**

Source: CFNZ Port CF 2020 Data Registry-Pharmac data on file received from supplier. Note: [#]Proportions are % of population with at least one F508del mutation. Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; 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.

Table 30 and Table 31, below capture the proportion of patients with each genotype in the 6 years and over and 12 years and over subgroups. As noted in section 4.1.1, *F/not yet characterised* patients have been apportioned 38% and 62% into F/RF and F/MF genotype groups, respectively. Patient number estimates also assume a 95% uptake rate (and 80% uptake for F/Gating patients switching from Ivacaftor – Respiratory Subcommittee record 3.57, August 2021), and discontinuation rates in the first year of treatment of 1.38% for F/F and F/MF mutations (Study 105) and 0.76% for F/RF, F/Gating and F/R117H mutations (Study 104).

Table 30 – Patient numbers for eligible CF patients 6 years and over

Population group	2022	2023	2024	2025	2026
Total CF patients 6 years and over	**411**	**419**	**427**	**435**	**443**
CF 6+ F/F	**194**	**198**	**202**	**206**	**210**
CF 6+ F/MF	**76**	**78**	**79**	**81**	**82**
CF 6+ F/RF	**33**	**33**	**34**	**35**	**35**
CF 6+ F/G	**13**	**13**	**14**	**14**	**14**
CF 6+ F/R117H	**16**	**16**	**16**	**17**	**17**
Total patients	**332**	**339**	**345**	**352**	**358**

Table 31 – Patient numbers for eligible CF patients 12 years and over

Population group	2022	2023	2024	2025	2026
Total CF patients 12 years and over	326	332	338	345	351
CF 12+ F/F	157	159	162	166	169
CF 12+ F/MF	58	59	60	62	63
CF 12+ F/RF	27	28	29	29	30
CF 12+ F/G	12	12	12	12	12
CF 12+ F/R117H	10	10	10	10	11
Total patients	264	269	274	279	284

5.3 Net Budget Impact to Pharmaceutical Schedule

The net impact to the hospital medicines list (HML) over 5 years is outlined in the Table 32 below. The net budget impact to the hospital medicine list estimates the cost of ELX/TEX/IVA based on a 95% adherence rate.

Displaced pharmaceutical cost assumes an 80% reduction in BSC pharmaceuticals – dornase alfa, hypertonic saline, nutritional supplements and tobramycin solution. The proportion of patients estimated to be taking these treatments has been estimated from Port CF NZ data (Port CF Data Registry, 2017). In addition, 80% of F/Gating patients on ivacaftor are assumed to switch to ELX/TEZ/IVA which amounts to approximately 4% of the total patient pool with any F mutation. The assumptions informing pharmaceutical savings were recommended by the Respiratory Subcommittee in their August 2021 meeting and are outlined in Table 32 below (Respiratory Subcommittee record 3.54 & 3.57, August 2021).

Table 32 – BSC Pharmaceutical cost assumptions

Item	Annual net cost	Annual net cost on ELX/TEZ/IVA	Estimated proportion of CF patients incurring the cost, on ELX/TEZ/IVA	Source
Dornase alfa	[redacted]	[redacted]	35%	(Port CF Data Registry, 2017)
Hypertonic saline	$795	$159	64%	“”
Nutritional supplements	$1,387	$277	43%	“”
Tobramycin solution	$2,568	$514	25%	“”
Ivacaftor	[redacted]	[redacted]	4%	80% of current F/Gating patients taking Ivacaftor

Table 33 – Net Budget Impact to the Pharmaceutical Schedule for CF patients 6 years and over

	Year					
Item	1	2	3	4	5	NPV
Patient numbers	332	339	345	352	358	-
Proposed pharmaceutical cost to HML	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Displaced pharmaceutical cost to HML	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Budget Impact to HML	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The net budget impact to the combined pharmaceutical budget if ELX/TEZ/IVA was listed for patients aged 6 years and over is [redacted] in the first year, with a total budget impact over 5 years of [redacted] (NPV 8%).

Table 34 – Net Budget Impact to the Pharmaceutical Schedule for CF patients 12 years and over

	Year					
Item	1	2	3	4	5	NPV
Patient numbers	264	269	274	279	284	-
Proposed pharmaceutical cost to HML	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Displaced pharmaceutical cost to HML	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Budget Impact to HML	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The net budget impact to the combined pharmaceutical budget if ELX/TEZ/IVA was listed for patients aged 12 years and over is [redacted] in the first year, with a total budget impact over 5 years of [redacted] (NPV 8%).

5.4 Net Budget Impact to DHBs

The net budget impact to District Health Boards (DHBs) is included in Table 35 and Table 36 below. DHB costs have been calculated to include savings to the health system as a result of reduced hospitalisations from PEx and reduced lung transplantations.

Hospitalisation and IV antibiotic health sector savings have been calculated using the proportion of people in the patient population who require these, and the average duration, in days, of hospitalisation (34% - 20.1 days) or use of IV antibiotics at home (19% - 18.2 days). These were sourced from a 2017 dataset provided by the CF data registry NZ ((Port CF Data Registry, 2017). The average daily cost of hospitalisation ($1,764) and home IV antibiotics ($189.8) outlined in section 4.5.3 was applied to calculate the estimated total cost of PEx for BSC patients without CFTR treatment. A 78% reduction is then applied to BSC PEx cost, to calculate the total cost of PEx for people receiving ELX/TEZ/IVA. This reduction is based on the PEx rate reduction of 0.22 from Study 102 (Middleton et al, 2019).

Lung transplantation costs have been calculated from the average annual number of CF lung transplants from 2016 to 2020 – 2.4 reported in a CFNZ stakeholder meeting with the supplier in March 2021. A 50% annual reduction in lung transplantation has been assumed, based on a French cohort study, noted by the Respiratory Subcommittee in August 2021, which reported a 50% reduction in the rate of lung transplantation for CF patients initiated on ELX/TEZ/IVA (Burgel et al, 2020) (Respiratory Subcommittee record 3.51, August 2021).

Table 35 – Net Budget Impact to DHBs for CF patients 6 years and over

	Year					
	1	**2**	**3**	**4**	**5**	**NPV**
Patient numbers	332	339	345	352	358	-
Net Budget Impact to HML	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact to other DHB costs (i.e. excluding pharmaceutical costs)	-$2,900,000	-$3,000,000	-$3,000,000	-$3,100,000	-$3,200,000	**-$13,100,000**
Net budget impact to DHBs total (i.e. including pharmaceutical costs)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The net budget impact to DHBs if ELX/TEZ/IVA was listed for patients aged 6 years and over is [redacted] in the first year, with a total budget impact over 5 years of [redacted] (NPV 8%).

Table 36 – Net Budget Impact to DHBs CF patients 12 years and over

	Year					
	1	**2**	**3**	**4**	**5**	**NPV**
Patient numbers	264	269	274	279	284	-
Net Budget Impact to HML	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact to other DHB costs (i.e. excluding pharmaceutical costs)	-$2,900,000	-$3,000,000	-$3,000,000	-$3,100,000	-$3,200,000	**-$13,100,000**
Net budget impact to DHBs total (i.e. including pharmaceutical costs)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The net budget impact to DHBs if ELX/TEZ/IVA was listed for patients aged 12 years and over is [redacted] in the first year, with a total budget impact over 5 years of [redacted] (NPV 8%).

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Appendix 1 – Supplier model review table

Model Input/ Assumption	**Questions**	Supplier details	Comment
Type of analysis	What type of analysis was undertaken (i.e., CUA or CMA)? Was this appropriate?	Four separate CUAs for relevant CF patients 6 years and older for the following genotypes – F/F, F/MF, F/RF and combined. Costs to health sector and health gains of the person measured in QALYs were generated using an individual patient microsimulation modelled in Microsoft Excel.	Appropriate. Due to the high quality of patient data available for cystic fibrosis patients, modelling the individual patient outcomes from CF treatment is appropriate. Moreover, the availability of registry data for people with CF in New Zealand enables country-specific validation of the model inputs and outputs, to further test the appropriateness of this approach. The model operates with a high level of granularity and complexity which is not easily reproducible in TreeAge and introduces a time burden for Pharmac review. However, Pharmac staff consider that the model functions correctly, delivering fit-for-purpose results.
Target population	Was the analysis based on the correct target population (i.e. the target population most likely to receive treatment, reflecting the clinical treatment algorithm and place in therapy in New Zealand)?	Target population: all CF patients aged over 6 years old with at least one F508del mutation.	Appropriate target population, though clinical advice received by Pharmac has noted the limited published evidence available in the 6 to 11 year old age group compared with 12 years and over. Consequently, Pharmac staff have created two separate proposals and accompanying economic analyses for the 6 years and over age groups and 12 years and over age group.
Treatment regimen (including dose)	Does the analysis describe all relevant treatment paths? Is the correct pharmaceutical dosage used? Are there likely to be dose adjustments (including frequency) over time? Does the analysis need to consider previous or subsequent lines of therapy?	No previous or subsequent lines of therapy were considered, beyond reversion to BSC for non-adherent patients. All patients on treatment take a twice daily dose of Trikafta. •Patients <30kg: 100mg (ELX), 50mg (TEZ), 75mg (IVA) in the morning and one tablet in the evening containing 75mg (IVA). •Patients >30kg: 200mg (ELX), 100mg (TEZ), 150mg (IVA) in the morning and one tablet in the evening containing 150mg (IVA).	Treatment pathway and dosage are considered appropriate, as is the decision to include no previous lines of therapy in the economic analysis. The adherence rate of 90% assumed by the supplier was considered inappropriately low, given the high health need and interest in treatment for the majority of the population (especially those who cannot access ivacaftor).
Comparator	Have the appropriate comparator(s) been used in the analysis? Is this the treatment that	For patients with an F/Gating genotype – best supportive care	The comparator was considered appropriate given available

Model Input/ Assumption	**Questions**	Supplier details	Comment
	most prescribers would replace in NZ clinical practice, and the treatment prescribed to the largest number of patients (if this differs from the treatment most prescribers would replace)? What is the current treatment paradigm? Does the analysis need to consider previous or subsequent lines of therapy?	(BSC) + ivacaftor, and BSC alone for all other patients	treatment options in the New Zealand context.
Efficacy	Is the model based on the best-quality data available? Were the sources of data used in the model clearly stated? Is there any evidence to suggest selective use of data? Is the primary evidence used adequately outlined?	The incremental benefit of ELX/TEZ/IVA is driven both by improvements in lung function (in terms of ppFEV1), weight-for-age z-score, and reduced pulmonary exacerbation (PEx) rates observed in the pivotal trials Studies 102 ,104, 105, 106 and 109.	Appropriate. All clinically significant outcomes were included and represented using the best available evidence, though Pharmac notes studies 105 and 109 used to inform patient outcomes in the modelling were unpublished and no evidence informing long term benefit beyond 96 weeks is currently available.
Time horizon and cycle length	Were the time horizon and cycle length appropriate and justified in terms of the underlying disease and the effect of interventions?	Lifetime. First two years of analysis: 4-Week cycle length From two years onward: 52-Week cycle length	Appropriate time horizon length, to capture the full duration of disease impacts which treatment seeks to address. Appropriate model cycle length. The four weekly cycle length is reasonable in order to capture clinical outcomes from the available clinical evidence, which is then extrapolated annually for the remainder of the model time horizon, where less granular data are available.
Health states and model structure	Has the model type (e.g. decision analytic model or Markov model) been described and justified? Is justification of the choice of health states within the model provided?	An individual state-transition patient simulation model was developed to evaluate the cost-effectiveness of ELX/TEZ/IVA used in combination with BSC for the treatment of CF in patients aged ≥6 years with at least one F mutation in the CFTR gene.	Appropriate. The individual state-transition model captures the heterogenous nature of CF and is able to capture benefit from changes in key clinical outcomes and surrogates, which influence health utility weight HRQoL and survival in the model.

Model Input/ Assumption	Questions	Supplier details	Comment
	Have any important health states been omitted from the model? If so, is this justified? Is the model transparent? Does the model appear to be unnecessarily complicated or simplified too much?	Although more computationally intensive than other state-transition models (i.e., Markov cohort models), the microsimulation structure is well-suited for modelling patients with CF, as it captures the heterogeneity of disease and tracks specific time-dependent patient characteristics which affect model outcomes (cost, disease severity, HRQoL, survival), and ultimately capture treatment effect on survival. The microsimulation is used to track CF disease progression and divergent outcomes by treatment, for individual patients over time. For each modelled comparison, two cohorts with identical baseline characteristics are simulated to estimate the costs and outcomes for patients treated with ELX/TEZ/IVA in the intervention arm and for the comparator – either BSC alone or a CFTR modulator. The genotype-specific simulated cohorts are derived from individual patient-level baseline data collected in the clinical trials of CFTR modulators. A total of 2,000 patient profiles are simulated for each treatment cohort, as this is the number of profiles needed to achieve stable model outputs (i.e., a negligible change in the cohort-level result was seen when simulating beyond 2,000 patients). Using identical cohorts ensures that any differences in modelled outcomes between the two cohorts are attributable to the treatment received rather than to differences in patient baseline characteristics.	The model is complicated and background functionality uses Excel macros, which are less immediately transparent than other approaches. However, Pharmac staff considered the complexity of the model to be warranted for modelling CF. Health states in the model are determined by lung function measured by ppFEV1% informing normal (≥90%), mild (89% to 70%), moderate (69% to 40%) and severe health states (≤40%). In addition, patients in severe health states have a probability of receiving a lung transplant and transitioning to a post-transplant health state. The states were considered to be defined with an appropriate level of granularity given the data available to parameterise the model.
Key parameters, transformation and extrapolations	Is the adaption of efficacy data into model inputs clear and adequately detailed? Does the analysis extrapolate data to the longer term, or extrapolate intermediate clinical endpoints to final outcomes? If so, is this appropriate, justified, and modelled using the correct	Acute treatment effects based on pivotal RCT evidence and ITCs (e.g. improved ppFEV1; reduced pulmonary exacerbations and improved weight-for-age z-scores) [Study 102, Study 104, Study 106, Study 109, ITC Appendix].	Appropriate. The acute improvements in clinical outcomes from the primary evidence captured in the model are clear and adequately detailed. Where indirect treatment comparison (ITC) was required, the Respiratory Subcommittee and PTAC noted the methods and

Model Input/ Assumption	Questions	Supplier details	Comment
	methodology? Was this tested in the sensitivity analysis?	Annual ppFEV1 decline is based on analyses of large longitudinal registry datasets (Konstan et al. 2007, de Boer et al. 2011, Sawicki et al. 2017).	results used for the ITC appeared reasonable.
	Have data from different sources been combined? If so, are the data compatible and combined using appropriate methodology?	Long-term reduction in the rate of ppFEV1 decline associated with CFTR modulator treatment was based on an Interim Analysis of Study 105 (see 3.1.8 Study 105 Week 96 Summary and TFLs; data cutoff date: 25 March 2021). This evidence supported the assumption of an 80% reduction in the long-term decline in ppFEV1 for patients treated with ELZ/TEZ/IVA.	Annual ppFEV1 decline assumed in the model is appropriate. It is consistent with clinical advice from the CF panel, who noted that the rate of decline in lung function is generally between 2-3% per year.
	Is there a clear and reasonable justification of how data have been incorporated into the model (i.e. the methodology used in the calculation of probability values)?	Individual patient characteristics (baseline values from the pivotal RCTs) were related to survival through a Cox proportional hazards model (Liou et al. 2001) which identified nine key characteristics of patients with CF that were found to predict survival: age, ppFEV1, gender, weight-for-age z-score, pancreatic insufficiency, diabetes, Staph aureus [Sa] infection, Burkholderia cepacia [Bc] infection, and number of acute exacerbations per year.	Pharmac notes significant uncertainty in the long-term benefit of ELX/TEX/IVA as the clinical evidence informing long term reduction in lung function decline includes only 96 weeks of unpublished interim data (Study 105). Interim analysis of Study 105 demonstrated that improvement in lung function for F/F and F/MF CF patients treated with ELX/TEX/IVA was maintained up to 96 weeks. In light of the uncertainty of long-term benefit beyond 96 weeks, Pharmac considers a reduction in lung function decline consistent with 80% to be appropriate and notes the Respiratory SAC's advice outlined in Section 4.3.
	Have the probability values been calculated accurately given cycle length?	The baseline hazard function for survival was derived from the parametric survival function that most appropriately fit the survival data from UK CF data registry (based on Akaike and Bayesian information criteria and clinical plausibility).*	The baseline hazard ratio applied to the survival curve for individual patients at the start of the model was informed by baseline characteristics in the UK CF registry. This was deemed appropriate since the CF panel and Respiratory Subcommittee (August 2021) noted that baseline characteristics in the UK registry are likely generalisable to NZ CF patients.
		*While the NZ CF registry (NZCFDR) report data on demographic information such as gender and age, as well as important clinical characteristics such as respiratory infections, lung function, and medical complications, it does not publish survival curves for CF patients by birth cohort in NZ. In the absence of patient-level, Kaplan-Meier	Survival gain has been estimated using the Cox Proportional Hazards (CPH) model estimated by Liou et al (2001) to model the relationship between surrogate markers and 5-year survival. Pharmac notes the supplier's commentary on the recent validation of the model – though the "CPH model has not been updated since its publication, the

Model Input/ Assumption	Questions	Supplier details	Comment
		survival data specific to NZ, international data were used to provide survival curves to model the current hazard of mortality over time for CF patients. Therefore, survival curves from the UK CF data registry (birth cohorts 1985–2008) were used to determine the baseline hazard of mortality in CF patients. These data were considered broadly generalisable to the NZ CF population, and this assessment was validated by comparison of the baseline characteristics in this dataset and in the NZ CF registry. A range of standard parametric survival distributions were tested to determine the most appropriate fit to these data based on Akaike and Bayesian information criteria. The resulting selection was validated by clinicians at an advisory board, and it was agreed that the Weibull projections for this UK population were clinically plausible (Vertex Pharmaceuticals Incorporated 2016).	authors presented an updated validation in 2015 of the logistic regression that was originally published alongside the CPH model in 2001 (Liou and Adler 2015). The updated logistic regression used US CFFPR data from 1993–2010. This analysis concluded that, while there were some slight changes to coefficients in the logistic regression model, the factors predicting mortality in patients with CF have remained stable". Pharmac considers that the CPH model is an appropriate means of approximating survival, given the large sample size in the dataset on which it is based, the stability of the coefficients over time and alignment of BSC mean and median life expectancies produced in the model with NZ estimates (noted by PTAC in record 10.13, November 2021). Pharmac notes that there remains uncertainty as to the magnitude of treatment benefit in terms of lung function decline and survival in the long term, but that this is due to limitations in available data not the methods used.
Health-Related Quality of life	How was quality of life measured? Was this method justified? If subjective values were used, were these validated and tested in the sensitivity analysis? Have New Zealand specific values been able to be sourced? If not from where and is/how is this justified? Were the estimated utility values reasonable? Have they been compared to those from other sources or diseases with similar qualitative impacts on quality of life?	Patient HRQoL utility weight is calculated according to the ppFEV1 stratum in which the individual simulated patient falls (i.e., normal [FEV1 >90%], mild [FEV1 70-90%], moderate [FEV1 40-70%] and severe [FEV1 <40%]). HRQOL in each stratum is defined using Australian utility weights generated from a email survey to 25 CF centre directors. Respondents were required to complete an EQ-5D questionnaire on behalf of their patients. The survey results reported a mean utility value for patients based on lung function, stratified by FEV, as follows: Normal (FEV>90%) = 0.98 Mild (FEV>70 to 90%) = 0.88 Moderate (FEV 40 to 70%) =0.67	The base case health utility weight values provided by the supplier were deemed inappropriate. Pharmac notes there are limitations with the small sample size of the clinician survey and that proxy estimates are likely to underestimate the health utility weight relative to patient-reported measures (Rand et al, 2015). The supplier base case health utility weights and utility weights estimated using regression equation provided by the supplier are considered appropriate for testing in the sensitivity analysis. Pharmac considers the treatment-specific utility increment to be appropriate. The Respiratory subcommittee noted that deriving health utility weights and health utility weight improvement on lung function alone does not capture the full multidimensional impact of CF on HRQoL and does not

Model Input/ Assumption	Questions	Supplier details	Comment
		Severe (FEV<40%)= 0.37 It is noted that the full impact of possible treatment effects on other body systems affected by CF is not captured by the EQ-5D utility weights above. In both Study 102 and Study 103 for ELX/TEZ/IVA and EXPAND for TEZ/IVA, treatment with CFTR provided substantial benefit across multiple non-respiratory domains of the CFQ-R, including physical functioning, social functioning, health perceptions, vitality, and treatment burden. None of these are captured by the utility weights above. To capture the full, non-respiratory benefits of treatment, a separate, treatment-specific utility increment was generated. The magnitude of this utility increment was derived from post-hoc analyses of pivotal studies, in which the CFQ-R-8D preference-based scoring algorithm was used to calculate health utility weight increment from the collected CFQ-R in Study 102 and 103 for patients on placebo and patients on ELX/TEZ/IVA. Regression analyses of these data demonstrated that ELX/TEZ/IVA provided a statistically significant treatment benefit over placebo, above and beyond what is explained by the ELX/TEZ/IVA ppFEV1 improvements. After adjusting for ppFEV1, a significant treatment-specific utility increment was observed for patients treated with ELX/TEZ/IVA (0.08; p<0.0001).	capture non-respiratory improvements in HRQoL likely associated with ELX/TEZ/IVA treatment. PTAC and the Respiratory Subcommittee noted that ELX/TEZ/IVA demonstrated clinically significant improvement in non-respiratory domains in the CFQ-R questionnaire in Study 102 and Study 103 and considered HRQoL measured using EQ-5D would reflect this.
Pharmaceutical cost	Were pharmaceutical costs calculated correctly? Were there any rebates that have not been included?	Pharmaceutical costs in the model are captured assuming a 90% adherence rate and a price drop in [redacted] one year after patent expiry. Patients are assumed to stay on ELX/TEZ/IVA treatment, at the full	Inappropriate adherence rate. The Respiratory Subcommittee noted adherence rates for patients on Tezacaftor/Ivacaftor of 92% and considered it was likely, due to ELX/TEZ/IVA superior efficacy, that patient adherence would be higher than 92%. Pharmac thus considers the suppliers

Model Input/ Assumption	Questions	Supplier details	Comment
	Is a generic pharmaceutical likely to become available in the near future? (see PFPA for more information) What dose was used in the cost calculations and where was this information sourced? (Note that the dose should be based on the dose used in the key clinical trials unless there is evidence of efficacy for different doses in clinical practice.) Are there likely to be dose adjustments over time (including frequency)? If relevant, was the correct bodyweight used in the calculation of pharmaceutical cost? Is there likely to be any pharmaceutical wastage? (This may occur due to inappropriate vial size, non-compliance, or if infusions cannot be stored once prepared).	dose, for the remainder of their lives, provided they are adherent at the time of treatment outset. The pharmaceutical costs for patients on BSC have been captured as outpatient cost estimates, informed by a CF health sector cost study (van Gool et al, 2013). Pharmaceutical costs on BSC are not assumed to change for patients treated with Trikafta. In addition, costs informed by the study by Van Gool et al have been converted to Australian dollars (in which they were originally gathered) and inflated using the Australian CPI index from 2009 to 2021, then converted to NZ dollars. F/Gating patients on ivacaftor and eligible to switch to ELX/TEZ/IVA have not been included in the model.	assumptions of 90% to be inappropriate and instead considers a 95% adherence to be more reasonable, with 90% and 100% tested in sensitivity analysis. The proposed pharmaceutical cost included a loss of exclusivity assumption and generic entry after [redacted], resulting in a price drop of [redacted] on the proposed net price in the base case. Pharmac considers this to be in line with the PFPA and an appropriate assumption. Pharmac consider the BSC pharmaceutical costs to be inappropriately captured. The respiratory subcommittee noted, due to ELX/TEZ/IVA mechanism of action enhancing CFTR activity in the body, mucolytic treatments such as dornase alfa and hypertonic saline would be reduced significantly along with antibiotic requirements. In addition, due to the significant improvement in Weight for Age Z scores in patients treated with ELX/TEZ/IVA, nutritional supplement requirements are also considered to reduce significantly. Moreover, costs from Van Gool et al were measured in Australia, and the PFPA 2.2 states that NZ-specific costs should be used where possible. Given the resource use data available in Van Gool et al. and publicly available list prices for the pharmaceuticals considered part of BSC, applying these prices to the pharmaceutical resource use was considered a more appropriate approach. Pharmac notes the F/Gating patients currently on Ivacaftor make up a small proportion of patients expected to start ELX/TEZ/IVA (~3.4%). Despite the likely more favourable cost

Model Input/ Assumption	Questions	Supplier details	Comment
			effectiveness of F/Gating patients switching from Ivacaftor to ELX/TEZ/IVA, the overall impact to the weighted average CUA result is likely to be immaterial given the size of the group. Excluding the subgroup is consequently considered prudent, and conservative in its impact.
Health sector costs	How is the pharmaceutical administered? Have all costs associated with administration been taken into account? Have primary health care costs been calculated correctly? (This should include both the patient co-payment and government contribution). Have hospital costs been calculated correctly using NZ DRG cost weights? Were these volume-adjusted? Are you aware of any costs that appear to be inaccurate? Have any important and relevant costs been excluded? Has this been justified? Do disease management costs differ between treatment and comparator? Has this been justified?	In the absence of NZ-specific cost data, the study by Van Gool and colleagues from Australia was used to estimate the cost of CF disease management (van Gool et al. 2013). Van Gool undertook a detailed study of the Australian costs of treatment for CF for all patients in the Australian Cystic Fibrosis Data Registry (ACFDR). Annual costs are reported from the perspective of the Australian health system and then converted to NZ dollars using a currency conversion rate of 0.9265 (March 2021 RBNZ). The costs tracked in this study include CF-related hospitalisations, prescription medications (see row above), medical services, dietary supplements, clinical visits, use of oxygen therapy, and pathology tests. Importantly, these costings preceeded the introduction of IVA in Australia and, therefore, provide an ideal source of resource use data associated with BSC for modelling purposes. Disease management costs are applied in the model by disease severity, defined by ppFEV1 thresholds, and are split by: setting (inpatient and outpatient) and whether costs related to PEx. Treatment with ELX/TEZ/IVA is assumed to reduce non-PEx related hospital costs by 81% compared to BSC (Feng et al. 2018). PEx-related event costs were not informed from Van Gool et al. Instead, a weighted average event cost was calculated based on AR-DRG-E60A and E60B hospitalisation cost data in 2015-2016, inflated and converted to	Health sector cost estimates related to inpatient and outpatient events were deemed inappropriate. Firstly, the supplier's method for inflating and converting costs to NZ dollars is not appropriate, as the costs outlined in Van Gool et al are converted from USD to AUD and inflated from 2009 to 2021 with an Australian inflation factor of 1.66 and then converted to New Zealand dollars. A more reasonable approach would be to first convert the costs in US dollars outlined by Van Gool et al to NZ dollars using a cost year exchange rate, and then inflate with a NZ inflationary factor from 2009 to 2021 of 1.22. In addition, the supplier has outlined that 26.6% of inpatient costs are non-exacerbation related (73.40% exacerbation related), and that these would reduce by 81%, informed by reduced admissions related to CF for ivacaftor patients from Feng et al. 2018. The supplier did not provide the studies which informed the 26.6% assumption and consequently Pharmac was unable to identify what events are captured as non-exacerbation related costs. It was also considered ambiguous whether costs would fall by 81% following an 81% reduction in admissions, since it was unclear whether the duration and intensity of hospital admissions fell in line with the number of admissions. PEx related event costs assumed by the supplier were deemed inappropriate. As previously mentioned, there are limitations with converting overseas cost data to NZ dollars. Pharmac NZ costings for DRG codes – E60A and E60B and so it is more

Model Input/ Assumption	Questions	Supplier details	Comment
		New Zealand dollars. The methods used to calculate the rates of lung	appropriate to use NZ cost estimates where possible. Pharmac deems the resource use outlined by Van Gool et al to be useful in informing costs for CF. Due to the issues with the supplier's approach, Pharmac has used the health sector resource use frequency of inpatient and outpatient services outlined by Van Gool et al. and applied the relevant NZ cost to these services.
Other related costs		The cost of the lung transplantation procedure was based on recent NZ data (Auckland DHB, 2021). It is estimated that around 69 CF patients received lung transplants over the 1993–2019 period (Auckland DHB, 2021) In the absence of New Zealand specific data the costs of medications and supplements required for the ongoing care of patients post-transplant have been taken from Australian sources. These costs have been inflated to reflect 2021 prices and converted to NZ dollars. AEs are considered to be acute conditions which result in a one-time cost. It is assumed that the majority of AEs captured in the model are managed by one additional GP visit. In some cases, it is assumed that a proportion of patients may require a specialist consultation and/or a pathology test. The impact of altering these assumptions on the cost-effectiveness of ELX/TEZ/IVA is negligible. The cost of ophthalmological visits, GP visits and LFTs is applied to patients receiving CFTR modulators. The tests	Lung transplant costs used in the model are appropriate. Pharmac was unable to identify New Zealand specific data for ongoing care costs post-transplant. The use of Australian cost data is appropriate in this setting as this cost was found to be largely immaterial to the analysis. The method for inflating and converting to NZ dollars was revised. The process undertaken to convert the AE frequencies to annual rates is not well explained, and it is considered possible that the costs of some more severe AEs might be better represented by hospitalisation costs. However, Pharmac staff have not further reviewed these, as they are ultimately not material to the analysis. CFT monitoring costs are appropriate and ultimately not material to the analysis.

Model Input/ Assumption	Questions	Supplier details	Comment
		include a liver function test for concentrations of AST, alanine transaminase (ALT), and bilirubin at three, six, nine, and 12 months after CFTR modulator initiation, as well as two ophthalmologist visits in the first year of initiation. In subsequent years, the only monitoring test performed is a liver function test (once annually). No additional physician visits are assumed to accompany the LFTs since CF patients are routinely monitored on a quarterly basis. The impact of altering these assumptions on the cost-effectiveness of ELX/TEZ/IVA is negligible.	
Results	Was the estimated r QALY per $1 million invested reported as a range as well as a point estimate? Were likely and possible range estimates provided? Were there any important factors that have been excluded from the analysis that could have an impact on the results? In your opinion, are the conclusions of the analysis justified? Is it reproducible, i.e., can the model results be reproduced from scratch?	Results were presented in QALYs/million.	Appropriate format. A point estimate in QALYs/million was provided along with a range of ICERs across a broad range of tested parameters. No key parameters which Pharmac considered material to the analysis were omitted from the CUA.
Discount rate	Was the correct discount rate (3.5%) used? Was the discount rate appropriately applied to both the costs and utility values? Was the discount rate appropriately applied to both arms of the model? Was the discount rate adjusted appropriately for the model cycle length? Has age of model entry been specified?	Costs and benefits are discounted at 1.03% per annum to reflect the current risk-free long-term government bond-rate (i.e., the 5-year government bond-rate as specified in Section 8.2 of the Prescription for Pharmacoeconomic Analysis v. 2.2 2015). Alternative discount rates of 0%, 3.5% and 5.0% are included in sensitivity analysis. Age of model entry is specified. No half-cycle correction is apparent.	Inappropriate. The PFPA's key recommendation for discount rates is to use a discount of 3.5% in the base case (Section 8.2.4). Currently all proposals considered by Pharmac are discounted by 3.5% in the base case. For consistency, this has been applied in the base case for ELX/TEZ/IVA. Pharmac staff considered that a half-cycle correction may have been appropriate, but was not included in the CUA.

Model Input/ Assumption	Questions	Supplier details	Comment
	Has a half-cycle correction been included? If not, what justification is given?		
Sensitivity analysis	Were all key inputs and assumptions varied in the sensitivity analysis (including those uncertain or with a material impact on outcomes)? Were the range and choice of variables used in the sensitivity analysis justified? Were the results of the sensitivity analysis interpreted correctly? Given the sensitivity analysis, are the chosen likely and possible CUA ranges reasonable?	A comprehensive range of sensitivity analyses were performed. These included analyses on discount rates, costs (including ELX/TEZ/IVA and BSC costs), treatment effects (including ppFEV1, PEx, WFAZ), utilities, compliance, discontinuation rates, the coefficients used in the Cox proportional hazard (CPH) mortality function and the mortality function itself.	Appropriate format and range of parameters tested. The sensitivity analyses were interpreted correctly. Pharmac considered it appropriate to exclude the discount rate sensitivity analyses from the likely or possible ranges, as these are informative scenarios to test but discount rate is not uncertain.
Analysis	Did the analysis list any factors that could limit the applicability of the results (e.g. differences in patient population) Were any caveats placed on analysis outcomes (e.g. awaiting further evidence appraisal or other events (e.g. pricing offers)? How could the analysis be improved? Describe the overall quality of the report.	*Operational validation of the economic model* The Weibull parametric survival function used in the base case analysis was compared to a range of other parametric survival distributions (Exponential, Weibull, Log-normal, Log-logistic and Generalised Gamma) and was found to be the best fit (according to AIC and BIC measures and plausibility of its projections) to the entire CF population in the UK (which was used as a proxy survival function in the absence of NZ-specific data). Furthermore, the Weibull function generated clinically plausible results (as determined by expert clinician review) when compared to the empirical survival estimates. *Comparison of the modelled output with empirical data* The model was further validated by comparing the median survival generated by BSC in the economic analyses with the estimated median survival predicted in New Zealand. In 2018 the life expectancy was estimated	Appropriate. Pharmac considers the economic assessment to be broadly appropriate, especially in relation to the modelling of treatment benefits, and notes the modelling approach submitted has been extensively used in decision modelling for CF. Clinical advice received from PTAC notes the uncertainty with the lack of long-term evidence available for ELX/TEZ/IVA and that when published long term evidence become available, long term benefit assumptions will require revision. The analysis could have been improved via inclusion of F/Gating CF patients taking ivacaftor plus BSC, considering the higher cost of ivacaftor and BSC compared with BSC alone. The model report submitted was well formatted and overall easy to understand.

Model Input/ Assumption	Questions	Supplier details	Comment
		at 37 years using PORTCF:NZ registry data (Personal communication, July 2021). To further validate the modelled estimates, the modelled survival curves were also compared with the survival of the general population in New Zealand (Figure 5.1.8). As shown in Figure 5.1.8, the model predicts similar baseline median survival for the F/F and F/MF populations (~38.2 years) compared to the median survival predicted from the PORTCF:NZ registry data (37 years). The model predicts a longer median survival for the F/RF population (45.3 years) compared with the 2018 estimate. This is expected as the F/RF patient population has a second CFTR allele that produces protein with residual function. As expected, the modelled ELX/TEZ/IVA and BSC survival curves show a lower life expectancy than the general New Zealand population. Further, this model has been validated by comparing its results with observed real-world data (McGarry, Lopez, Chandler, et al., 2020). The results of this peer-reviewed published validation study suggest that the model methodology produce an accurate reflection of the real-world impact of CFTR modulators. In addition to this, the model has been assessed and used to inform reimbursement decisions for multiple HTA bodies globally and is based on the model that PHARMAC used to assess IVA. Given the inherent uncertainty in projecting the survival of future cohorts of persons with CF the impact on the cost-effectiveness of ELX/TEZ/IVA of varying a range of parameters that underlie these survival estimates are tested in sensitivity analyses	